ADHERENCE TO INR MONITORING IN THE COMMUNITY AMONG VKA-TREATED PATIENTS IN SASKATCHEWAN : AN OBSERVATIONAL STUDY

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ABSTRACT

Background:

Vitamin-K antagonists (VKA) are a class of oral anticoagulant medications used to prevent blood clots. The anticoagulant intensity of VKAs is measured with a blood test known as the *International Normalized Ratio* (INR). Traditionally, international guidelines have recommended INR tests every 4 weeks for all patients. However, adherence to these guidelines has never been investigated in real world settings. The objectives of this study were to describe adherence to INR testing in Saskatchewan among patients receiving VKA medications, and to identify predictors of optimal adherence.

Methods:

This was a retrospective cohort study of VKA users in Saskatchewan captured in the administrative data between 2003 and 2010. Physician claims for anticoagulation monitoring were used as a proxy for INR testing. Adherence to INR testing was measured using the *Continuous, Multiple-Interval Measure of Medication Gaps* (CMG). Individuals were considered adherent if adherence by the CMG was at least 80%. Hierarchical (random effects) logistic regression models were developed to identify important predictors of optimal INR monitoring. Individual physician identification was considered a random effect in these models. The dependent variable was the achievement of optimal adherence, defined as ≥80% adherence to the 4-week test interval.

Results:

Among 17,388 VKA users, 42% resided in rural areas and virtually all (99%) were monitored by a general practitioner. During a median follow-up of 514 days, 50% of patients exhibited at least 74% adherence to INR testing if a 4-week interval was used as the reference standard. However, the estimated median adherence increased dramatically to 98% when the benchmark for optimal testing was lengthened to every 12 weeks. The most prominent risk factors for poor adherence to INR monitoring appeared to be rural residence (rural vs. urban OR 0.55, 95% CI 0.47-0.64 among subjects age ≥75 years) and duration of VKA therapy (≥731 vs. 35-90 days OR 0.04, 95% CI 0.03-0.05).

Discussion:

Adherence to INR testing appeared to be acceptable for most VKA-treated patients in Saskatchewan. However, this data indicated that adherence might be more problematic in the subgroup of rural residents. Possible explanations include reduced access to testing facilities or the shortage of physicians in rural areas. Further research is required to understand if poor access is the underlying cause of non-adherence to INR testing in the rural population.

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LIST OF ABBREVIATIONS

ACC	anticoagulation clinics
AF	atrial fibrillation
CCB	calcium channel blocker
CCI	Canadian Classification of Health Interventions
CJRR	Canadian Joint Replacement Registry
CMG	Continuous, Multiple-Interval Measure of Medication Gaps
CV	cardiovascular
DAD	Hospital Discharge Abstract Database
DF	degrees of freedom
DVT	deep vein thrombosis
ER	emergency room
GI	gastrointestinal
ICC	intraclass correlation coefficient
ICD-9	International Classification of Disease, Ninth Revision
ICD-10-CA	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada
ICH	intracranial hemorrhage
INR	International Normalized Ratio
ISI	International Sensitivity Index
LMWH	low-molecular weight heparins
LRT	likelihood ratio test
MSB	Medical Services Database
NOAC	new oral anticoagulant medications

NSAIDs	nonsteroidal anti-inflammatory drugs
OR	odds ratio
PDP	Prescription Drug Database
PE	pulmonary embolism
PHRS	Person Health Registration System
PHV	prosthetic heart valves
PT	prothrombin time
RAAS	Renin-Angiotensin-Aldosterone System
SD	standard deviation
TTR	time in the therapeutic range
UC	usual care
V_A	area level variance
VIF	variance inflation factor
VKA	vitamin K antagonists
VS	Vital Statistics
VTE	venous thromboembolism
VTEP	prevention of venous thromboembolism

1 INTRODUCTION

1.1 Rationale

For over 60 years, vitamin K antagonists (VKAs) such as warfarin have been the best options to manage patients requiring long-term anticoagulation (1). However, despite its therapeutic importance, warfarin is responsible for a large proportion of hospitalizations due to adverse drug reactions (2,3). Recently, new oral anticoagulant medications (NOACs) have become available that are not dependent on lab monitoring for maximizing efficacy and safety. Consequently, the roles of VKAs are being seriously re-examined, in particular because of their additional requirement for ongoing venous blood testing to monitor each individual's level of anticoagulation with the INR (*International Normalized Ratio*) (4). Despite extensive research into requirements for monitoring and target INR values, little is known about patterns of INR testing and their contribution to patient outcomes in real world settings.

1.2 Purpose

The purpose of this report is to quantify adherence to INR testing recommendations and identify predictors of optimal adherence among VKA-treated patients in Saskatchewan.

1.3 Objectives

1. *Describe INR monitoring patterns and determine adherence to international guidelines*
2. *Identify predictors of optimal adherence to INR monitoring*

1.4 Study Hypotheses

Objective 1

The frequency of INR monitoring (as measured by the *Continuous, Multiple-Interval Measure of Medication Gaps)* among VKA users in Saskatchewan will not meet international guideline recommendations.

Objective 2

The most significant predictors of optimal adherence to INR monitoring will be older age, urban residence, prior stroke, and a diagnosis of atrial fibrillation or prosthetic heart valve replacement.

2 LITERATURE REVIEW

Medline was used to search for literature generally related to the research question, using a variety of keywords pertaining to adherence, VKA therapy, and INR monitoring. The reference lists of anticoagulation guidelines were reviewed, as well as those of the relevant papers identified.

2.1 Vitamin K Antagonists and the International Normalized Ratio (INR)

VKAs are oral anticoagulants that reduce the production of vitamin K dependent clotting factors in the liver. By reducing the concentration of circulating clotting factors, VKAs essentially reduce the efficiency of the clotting process in the body. As a result, these medications can be used to prevent the formation of clots (thrombi) as well as speed the degradation of existing clots that are associated with adverse health effects. However, in contrast to their beneficial effects, VKAs can also cause serious bleeding events. The risk of bleeding with VKA therapy is highly influenced by their unpredictable pharmacokinetic properties (1) coupled with numerous food and drug interactions (5). As a result, patients receiving VKAs require regular blood testing to ensure that adequate anticoagulation is achieved with minimal risk.

The basis for measuring the intensity of anticoagulation is the test of prothrombin time (PT). The PT test represents the time to clot formation in a sample of blood after the addition of promoters such as calcium and thromboplastin. Because PT is sensitive to changes in the concentration of clotting factors, it adequately measures the degree of anticoagulation produced by warfarin and other VKAs (1,6). Due to a high level of variability between different thromboplastins (i.e., clot promoters) used in PT tests, the international sensitivity index (ISI) was created to standardize the PT to a common international reference, the *International Normalized Ratio* (INR). The INR represents the anticoagulant activity of VKAs in a manner that allows comparison between different laboratories (1).

For the majority of VKA-treated patients, an INR below 2.0 has been associated with an excess risk of thromboembolism (7), whereas an INR above 3.0 is associated with an unacceptable risk for bleeding (1,8,9). Although strict monitoring of VKAs in clinical trials has demonstrated that they can be used safely and effectively (10,11), it is not known whether the

generalizability of these highly controlled conditions can be consistently applied to real world settings (12–15). Not only do patients have to take the VKA regularly but they also must travel to a recognized laboratory on a monthly basis to ensure proper monitoring occurs. These requirements make the use of VKAs relatively more complex than typical medications used in outpatient settings; thus the potential for non-adherence to INR monitoring in real world settings is high.

2.2 Major Indications for Anticoagulation

VKA therapy is indicated for the prevention and treatment of thromboembolism among patients with atrial fibrillation (AF) (16,17), venous thromboembolism (VTE) (18), prosthetic heart valves (PHV) (19), and those undergoing orthopedic surgeries and other related procedures (VTEP) (20).

2.2.1 Atrial Fibrillation

Atrial fibrillation (AF) is a heart arrhythmia that increases the risk of cardioembolic stroke. In these patients, ineffective atrial contractions can lead to pooling of blood and thrombus (clot) formation within the atrium itself. These thrombi can dislodge, travel through the arterial circulation, and eventually lodge in cerebral blood vessels causing a stroke (21).

Altogether, AF contributes to approximately 15% of all occurrences of stroke worldwide (16), of which a substantial proportion are disabling (22). Although the prevalence of AF is 0.4% to 1% in the general population (21,23,24), age is a major risk factor for AF such that its prevalence increases to approximately 10% in those 80 years and older (16,24). The median age of AF patients is approximately 75 years, and an estimated 70% of all cases are between the ages of 65 and 85 years (23).

AF is commonly associated with structural heart diseases, including heart failure, coronary artery disease, hypertension, and valvular heart disease. *Nonvalvular* AF refers specifically to the disease in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve disease (21). Valve disease further increases the risk of stroke with AF. In the Framingham Heart Study, AF associated with rheumatic heart disease increased the risk of stroke 17-fold compared with age-matched controls, and only 5-fold without rheumatic heart

disease (25). However, *valvular AF* contributes to a small proportion of the overall AF population (26,27).

The risk for stroke in patients with nonvalvular AF is modified by the presence of additional independent risk factors. A simple risk stratification scheme called the $CHADS_2$ risk score is often used by healthcare professionals to estimate an individual patient's risk of stroke from AF. Risk factors in this scheme include: heart failure, hypertension, age 75 or greater, diabetes mellitus, and prior stroke or transient ischemic attack (carrying double the risk). In patients with AF the annual rate of stroke ranges from 1.9% (95% CI 1.3 to 1.7%) to 18.2% (95% CI 10.5 to 27.4%) depending on the number and type of risk factors present (28). Given the variable risk of stroke associated with AF, not every patient will experience a net benefit from anticoagulation therapy. Therefore, VKA therapy is indicated only when one or more risk factors for stroke are present in addition to AF. In these cases, lifelong therapy is usually recommended at a target INR range between 2.0 to 3.0 (16,17,29).

For the primary prevention of stroke with AF, dose-adjusted warfarin provides approximately a 2.7% absolute reduction in the annual risk of stroke compared to placebo. In the secondary prevention of stroke, warfarin provides an annual risk reduction of 8.4%. Overall, warfarin provides about a 64% (95% CI 49% to 74%) relative risk reduction in stroke compared to placebo. Furthermore, compared to antiplatelet therapy, warfarin provides an additional 39% (95% CI 22% to 52%) reduction in risk (22).

2.2.2 Acute Venous Thromboembolism

Venous thromboembolism (VTE) is a disease encompassing both deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is a condition resulting from an apparent inappropriate clot formation in the deep veins of the leg. These large clots can produce swelling, pain, and even long term damage to the veins themselves. Similar to AF, these clots can break apart or dislodge and travel up the venous circulation until getting wedged in a pulmonary artery, blocking oxygen transfer by the lung. This situation is termed a PE and can be fatal in a high proportion of cases. Although VTE can occur in young, otherwise healthy individuals, they are more frequent when risk factors are present (30,31). These include multiple trauma, major surgery, prolonged immobilization, and hypercoagulable disorders amongst others (6). The

annual incidence of symptomatic VTE is approximately 0.1% in the general population, and increases with age (32).

Following an acute episode of VTE, immediate and full anticoagulation is required to prevent thrombus extension and embolization (6). In addition, continued VKA therapy is required to reduce the risk of future events (30). The risk of a second VTE is lowest when the initial event occurred in the presence of a major transient risk factor such as surgery, hospitalization, or cast immobilization (30). It has been estimated that the rate of recurrence is only 0.7% per year after stopping anticoagulant therapy for a VTE associated with a surgical risk factor; while VTE recurrence associated with a non-surgical risk factor is estimated to be 4.2% per year (33). The risk of VTE recurrence is highest, however, when there is no identifiable risk factor associated with the initial event (i.e., unprovoked) (33,34). The rate of recurrence, in this case, is estimated to be 7.4% per year; corresponding to a rate ratio of 2.5 (95% CI 2.0 to 3.2) at 1 year compared to a VTE provoked by any transient risk factor (33). It is for these reasons that only 3 months of anticoagulation with a VKA is recommended following a VTE associated with a transient risk factor, while indefinite treatment may be required following an unprovoked VTE. In both cases, however, the target INR is between 2.0 to 3.0 (18).

The effectiveness of VKA therapy in the treatment of VTE is well demonstrated by trials comparing short-term anticoagulation, for 4 or 6 weeks, to intermediate durations of 3 or 6 months. Extending the duration of anticoagulation reduces the risk of recurrent VTE by approximately one half (RR 0.53, 95% CI 0.40 to 0.70) (30).

2.2.3 Prevention of Venous Thromboembolism

Venous thromboembolism is a major complication in hospitalized patients undergoing major orthopedic surgery (total hip or knee replacements and hip fracture surgery). Without thromboprophylaxis, the incidence of symptomatic VTE following total hip replacement is estimated to range between 2% to 5%, and fatal PE occurs at a rate of 0.1% to 2.0% (31).

Adjusted-dose warfarin, to a target INR between 2.0 to 3.0, is one option recommended for primary thromboprophylaxis after major orthopedic surgeries (20). In this role, VKAs have been estimated to reduce the risk of DVT by 44% (RR=0.56, 95% CI 0.37 to 0.84) and the risk of clinical PE by 77% (RR=0.23, 95% CI 0.09 to 0.59). Another class of anticoagulants, low-

molecular weight heparins (LMWH), are even more effective than VKAs for this indication, but have to be administered by injection (31,35). Regardless of which anticoagulant is used, thromboprophylaxis is only required for 10 to 35 days after orthopedic surgeries (20).

The Canadian Joint Replacement Registry (CJRR) reports that between 2003 and 2007 there has been a substantial decline in the use of warfarin following major orthopedic surgeries (from 39% to 22% of hip replacements, and from 39% to 25% of knee replacements). During the same time period, the use of low-molecular weight heparins has increased from 65% to 74% following hip replacement surgeries, and from 63% to 73% following knee replacements. The CJRR report suggests that this might be explained by the need for INR monitoring with warfarin therapy. Furthermore, blood monitoring has likely become even less desirable as the length of hospital stays has decreased following joint replacement surgeries (36).

2.2.4 Prosthetic Heart Valves

Valve replacement, with either mechanical or bioprosthetic valves, is indicated in the treatment of numerous congenital and acquired valvular heart diseases (37,38). The prevalence of valve disease is approximately 2.5% in the general population, and increases with age. Between the ages of 18 to 44 years, the estimated prevalence is 0.7%, rising to 13.2% for those 75 years and older (39).

Mechanical prosthetic heart valves are associated with a lifetime risk of thromboembolic complications, estimated to be as high as 22% per year with no anticoagulation (40). However, an individual's risk for thromboembolic events varies with the valve position and the type of prosthetic used (40). The annual rate of thromboembolism among anticoagulated patients has been estimated to be 0.5% with bileaflet valves, 0.7% with tilting-disk valves, and 2.5% with caged-ball or disk valves. The corresponding annual rate with valves positioned in the aortic position is 0.5%, increasing to 0.9% in the mitral position, and to 1.2% with valves in both positions (41).

The American College of Chest Physicians recommends life-long anticoagulation with warfarin, at a target INR between 2.0 to 3.0, for most mechanical valves in the aortic position. This target is increased to 2.5 to 3.5 for most valves in the mitral position, given the higher thromboembolic risk they carry (19). While the recommended INR range for the less commonly

used caged-ball valve is also 2.5 to 3.5 (40), it has been suggested that the optimal range may be as high as 4.0 to 4.9 (41).

Unlike mechanical valves, the rate of thromboembolic events with bioprosthetic valves is only high in the first 3 months following surgery, but decreases thereafter (42). For this reason, guidelines only recommend anticoagulant therapy for the first 3 months following replacement with a bioprosthetic valve in the mitral position (19).

2.3 Bleeding Risk with Vitamin K Antagonist Therapy

Although VKAs effectively reduce the risk for thrombus formation, they also increase the risk of bleeding (1). Bleeding is the most common and severe complication associated with anticoagulant therapy (43,44). *Major bleeding* is of particular interest, and includes events that are fatal, life-threatening, result in long-term complications, or consume considerable healthcare resources (44). There is a special emphasis on the occurrence of intracranial hemorrhages (ICH) (43) because these are much more likely to result in death or disability compared to extracranial hemorrhages ($p<0.001$), and are associated with approximately a 50% case fatality rate (45). However, the most common major bleeding events associated with VKAs originate from the gastrointestinal (GI) tract. These GI bleeds account for approximately 60% of all cases of VKA bleeding (8,13).

In a pooled analysis of early clinical trials, the rate of major bleeding was 1.3% per year with warfarin therapy compared to 1.0% per year with placebo. The corresponding annual rates of ICH were 0.3% and 0.1%, respectively (46). Similar results were observed in a large observational study, which reported annual rates of 1.5% for major bleeding and 0.5% for ICH (13). The rate of bleeding is substantially increased by several risk factors, however, including the intensity of anticoagulation (i.e., level of INR), the length of therapy, certain patient characteristics, and interacting medications (43).

The risk of bleeding at different anticoagulation intensities was evaluated in a recent meta-analysis. This study observed that the absolute risk of major bleeding increased from 1.4% per year at an INR of 2 to 3, to 3.7% per year at an INR of 3 to 5 (9). The risk of bleeding has also been found to be highest near the beginning of therapy (43), as demonstrated by an observational study that found approximately a three-fold increased risk of bleeding in the first 3

months of therapy (12). Age has also been commonly associated with bleeding risk (43). Observational studies have found that bleeding risk is increased two to three-fold in patients 80 years of age and older (12,47). Lastly, the risk of bleeding is increased with the concurrent use of several interacting medications (43). A large cohort study observed that bleeding risk was nearly doubled when warfarin was used in combination with aspirin (HR 1.83, 95% CI 1.72 to 1.96), tripled when used in combination with clopidogrel (HR 3.08, 95% CI 2.32 to 3.91), and nearly quadrupled when all three medications were used together (HR 3.70; 95% 2.89 to 4.76) (48).

2.4 Monitoring Vitamin K Antagonist Therapy

2.4.1 Frequency of INR Monitoring and Time in Therapeutic Range (TTR)

The dose-response relationship with VKAs is very poor. Therefore, when a VKA is newly initiated, frequent INR monitoring is necessary to determine the appropriate daily dose for each individual. Generally this involves monitoring several times per week for the initial 1 to 2 weeks of therapy, and reducing the frequency based on the stability of results. Until recently the American College of Chest Physicians recommended monitoring at an interval of no longer than 4 weeks for the duration of VKA therapy once a stable dose has been achieved (1). However, the most recent anticoagulation guidelines suggest that patients with a stable INR may be safely monitored at intervals as long as 12 weeks (49). More frequent monitoring should be undertaken to investigate aberrant values or to monitor after changes to the patient's medication regimen, diet, or health status (1).

In clinical settings, the frequency of INR monitoring highly influences the quality of anticoagulation control, as measured by the time in the therapeutic range (TTR) (50–53). The TTR is the proportion of days spent within the target range, estimated by interpolating INR values between consecutive tests (54). A systematic review found that studies with frequent INR monitoring achieved a greater proportion of time in the target range (53). VKA-treated patients undergoing INR testing every 3 weeks spend approximately 48% of the time in therapeutic range, compared to only 41% in patients tested every 5 weeks ($p<0.0005$ for trend) (52).

However, there have also been studies suggesting that there is little difference in anticoagulation control at monitoring intervals as long as every 14 weeks (55–58). The most

recent of these was a randomized trial of patients with a stable INR, comparing dose assessment every 4 weeks to every 12 weeks. Ultimately they observed no significant difference in TTR between the two groups after one year of follow-up (74.1% vs. 71.6%, p=0.020 for noninferiority). However, the patients that were monitored every 12 weeks still underwent blood testing every 4 weeks and had regular follow-up with the staff at the anticoagulation clinic. The only difference was that sham INR results, within the therapeutic range, were reported to the staff for 2 out of every 3 tests. The extent to which regular patient contact influenced adherence and outcomes in this study is unknown. Also, patients were only eligilble if they did not require any dose adjustments within 6 months prior to the study (i.e., stable). This comprised approximately one-third of patients attending their clinic (55), meaning that these results do not apply to the other two-thirds of patients that would still require traditional frequencies of blood testing. However, this study provides preliminary evidence that less frequent monitoring may be equally as safe and effective.

Ultimately, the extent to which the INR is kept in the therapeutic range over time is strongly associated with clinical outcomes in patients treated with warfarin (41,50,59,60). Patients achieving poor INR control are at greater risk of adverse events compared to those who are better controlled (61–63). In a cohort of patients with VTE, the quartile with the worst INR control (TTR <45%) experienced nearly a three-fold risk of recurrent VTE and major bleeding than patients in the two highest quartiles of INR control (TTR 65-80% and 80-100%) (61). Another study reported that among patients with AF, a 10% increase in time spent out of range significantly increased the risk of all-cause mortality (OR 1.29, p<0.001), ischemic stroke (OR 1.10, p=0.006), and thromboembolic events (OR 1.12, p<0.001) (59). Ultimately, anticoagulation control determines the safety and efficacy of VKAs and is a major consideration when comparing VKAs to new oral anticoagulant medications (NOACs)(62,63).

2.4.2 The Effect of Monitoring Setting on Anticoagulation Control

Patients on anticoagulation therapy are usually monitored by either specialized anticoagulation clinics (ACCs) or by physicians in usual care (UC). ACCs generally focus on the management of anticoagulation only, leaving the patient's other medical issues to their primary care physician(s) (64,65). There are five anticoagulation clinics offered in Saskatchewan, located within the Saskatoon, Regina Qu'Appelle, Five Hills, and Kelsey Trail

Health Regions (66, Lamb, Darcy. Personal communication. 2014 October 20). The remainder of anticoagulated patients in the province continues to be monitored by prescribers not affiliated with ACCs.

Meta-analyses of studies evaluating anticoagulation control have consistently demonstrated superior INR control in ACCs (53,67,68). Van Walraven et al. reviewed 67 studies evaluating anticoagulation therapy for any indication, and determined that the mean TTR achieved in community practice was significantly lower compared to ACCs (56.7% vs. 65.6%; difference -8.3%, 95% CI -4.4 to -12.1%) (67). Dolan et al. performed a similar analysis on 22 studies evaluating patients with AF, and again found that patients managed in ACCs spent significantly more time in therapeutic range (mean TTR 63.6% vs. 52.3%; difference 11.3%, 95% CI 0.1 to 21.7%) (53). A meta-analysis of 6 AF studies conducted in the United States, similarly observed that patients managed in UC spent on average 51% of their time in therapeutic range compared to 63% in ACCs (difference -11%, 95% CI -2 to -20%) (68).

Given the consistent evidence in favor of anticoagulation clinics, the American College of Chest Physicians recommends systematic and coordinated monitoring in a manner similar to that provided by ACCs (1,49). However, monitoring of anticoagulation is still the responsibility of usual care physicians in most parts of the world (64). In Canada, it has been estimated that as many as 95% of anticoagulated patients are managed in UC (69), and that the majority of the physicians involved practice in family medicine (64). For this reason, information on the quality of INR monitoring in UC is of particular interest.

2.4.3 INR Monitoring in Usual Care (UC)

VKA-treated patients mostly require INR testing at least every 4 weeks for the duration of their treatment, although stable patients may be monitored as infrequently as every 12 weeks (1,49). Although many studies report a high frequency of INR testing among VKA-treated patients (52,59,64,65,69–81), the vast majority of these settings do not appear to reflect real world practice. In managed care programs, INR testing has been carried out at a frequency of every 18 to 22 days (70,71). Similarly, a mean interval of 15.7 days (SD 18.1) has been reported in the academic setting (59). Other studies conducted in UC have found that approximately 80% of patients were monitored at least monthly (52,72,82), and others have reported that patients undergo on average at least one INR test per month (73–75,77,82).

Overall, the literature suggests that patients are usually monitored at the frequency recommended by treatment guidelines. However, these reports may not be generalizable to busy community practices. For instance, all randomized trials (76,81,83–85) and several observational studies have required patient or physician consent prior to enrolling patients (64,69,72,86–88). Furthermore, a number of the population-based studies have collected data from commercially insured populations (52,70,71,73–75) and academic centers (59,65,77,89,90). These settings may provide care in a more coordinated manner, so the high frequency of INR monitoring may not be representative of real world practice.

Another explanation for the higher rates of monitoring observed in some of these studies is the measures that were used. The calculation of a mean interval or a mean number of tests per month does not account for more frequent monitoring as a result of out-of-range values. Consequently, a period of more frequent testing could falsely increase the overall estimate of adherence to INR monitoring.

2.4.4 Adherence to INR Monitoring

The responsibility for adhering to chronic medication regimens ultimately falls on individual patients in most outpatient healthcare settings. Unfortunately, the prevalence of non-adherence is known to be extremely high regardless of the type of medication prescribed (91). In addition to the requirement for medication adherence, VKA users are also required to regularly visit a community or hospital laboratory to undergo INR testing. As a result, any patient receiving VKA therapy has an opportunity to be non-adherent to the drug and/or the ongoing testing of INRs. The high frequency of INR testing among VKA-treated patients reported in published studies (52,59,64,69–77) is surprising given the extent of non-adherence to chronic medications overall (92). In addition to the usual barriers to adherence (91,93), it is likely that INR testing has specific barriers such as the discomfort of routine venipuncture (67) and inconvenience, especially in rural settings where the distance to a laboratory might be great.

There are three retrospective studies that suggest that non-adherence to INR monitoring may be a problem. The first study observed 40 patients with stable anticoagulation, whose monitoring was transitioned from an ACC to UC (78). In this process, the median time to the first INR measurement in UC was 41 days. However, more surprising was the observation that three patients did not have a single INR test in the 6 months of follow-up in UC. Furthermore,

these patients had received extensive education stressing the importance of regular INR testing while they were managed at the ACC, suggesting that patients lack the ability to direct their own care. However, this study had a small sample size (n = 40) and every patient had initially been managed in an ACC (78). This suggests the possibility that adherence to INR monitoring could, in fact, be even worse in the real world.

A large population-based study in Ontario has also indicated that there may be a high prevalence of non-adherence to INR monitoring (8). This study captured patients exposed to oral anticoagulant therapy using administrative databases, and subsequently assigned them to periods of 'monitored' and 'unmonitored' VKA exposure. Patients were considered 'unmonitored' when there was an interval greater than 8 weeks in duration between consecutive INR tests. Ultimately, they found that patients were 'unmonitored' for 48.5% of the time they were considered to be taking warfarin. This suggests that a substantial proportion of monitoring intervals were greater than 8 weeks in duration. However, the authors point out that because the bleeding rates were similar in patients that were unmonitored and those that were unexposed to warfarin (1.9 vs. 1.8 events per 100 patient-years), it is possible that a large proportion of the unmonitored VKA exposure was a result of temporary discontinuation of therapy (8). An older study similarly observed that 53% of testing intervals exceeded 12 weeks in the UC setting. However, this was a single-center study evaluating a relatively small group of patients (n=145) (89).

2.4.5 Predictors of Adherence

The risk factors for non-adherence to INR monitoring have not been substantially investigated in the literature. Furthermore, current evidence comes from single-center studies of specialized clinics (94), also enrolling a small number of subjects (95,96). Given these limitations, very little information is available to understand the predictors of adherence to INR monitoring guidelines in the general population. The adherence literature is typically focused on predictors of adherence to medication use. In fact, a large body of literature has investigated the predictors of adherence to cardiovascular medications. Although the relationship between adherence to INR monitoring and adherence to cardiovascular medications is unknown, these studies may serve as a useful guide to derive hypotheses about possible factors that may be important.

Demographic factors that have mostly been associated with good adherence to cardiovascular (CV) medications include increasing age (94–99) (which has also demonstrated a U-shaped relationship (100)), male sex (97,99–101), and higher income (97,100). There has been less consistent evidence to support that a high utilization of healthcare services is a predictor of good adherence to CV drugs (95,100–102); however, there are reports of an association between adherence and a high frequency of physician visits both before (98,103) and after (97) the start of therapy.

General comorbidity has been inconsistently associated with non-adherence to CV medications (95,97,101,102); however, there are several specific disease states more commonly associated with improved adherence. These include a history of diabetes or use of antihyperglycemic agents (97,98,100,102,103), and also prior stroke or transient ischemic attack (TIA) (96,99,102). In general, it appears that in the case of statin medications (a cholesterol-lowering medication), the concurrent use of other CV medications is associated with good adherence while noncardiovascular medication use is associated with poor adherence (97,98,100).

Despite the critical importance of INR monitoring for successful (and safe) use of VKA medications, little information is available to understand the predictors of monitoring outside of specialty clinic settings. For example, the effect of rural residence may be an important predictor of less frequent INR monitoring due to laboratory accessibility and/or availability of healthcare providers. Individuals living in rural settings may have to travel great distances to access laboratory testing facilities. Alternatively, the shortage of rural physicians (104,105) could result in less strict monitoring or slower response to undesirable test results. Although limited access to healthcare providers in rural settings is an important barrier to successful chronic disease management overall (105), the situation is especially problematic for patients receiving warfarin (or other VKA medications). Failure to ensure regular testing or failure to act upon testing results can lead to therapeutic failure (i.e., thromboembolic events) or adverse event (i.e., bleeding due to over-anticoagulation) in VKA users (59,61).

Knowledge about INR testing and its underlying determinants are important for several reasons. For example, NOACs have recently become available in Canada with the advantage of predictable dose-response activity, eliminating the need for anticoagulation testing altogether (4).

However, coverage for these medications in Saskatchewan has been restricted due to their extremely high cost compared to VKA medications (i.e., considering drug costs only)(106). The rationale for restricting NOAC coverage in Saskatchewan was partly based on the assumption that equivalent therapeutic benefits can be achieved with VKA medications if INR control is optimal. Presumably, the achievement of optimal INR control requires consistent monitoring; thus greater awareness of the predictors of INR monitoring will help inform policy regarding coverage of NOAC agents.

2.5 Summary

The frequency of INR testing is known to influence anticoagulation control. Ultimately, the extent to which a patient stays in the target range is associated with the risk of bleeding and thromboembolism (59). The current literature mostly reports a high frequency of INR monitoring in typical community practice (52,59,64,69–77); however, many of these studies originated from targeted providers or institutions and it is doubtful that they represent usual care settings. Adherence to chronic medications is notoriously poor (92), and adherence to INR monitoring may be influenced by similar barriers. To our knowledge, adherence to INR monitoring has never been explored in real world settings.

3 METHODS

3.1 Data Source

The Saskatchewan Ministry of Health collects and maintains health-services data for residents in the province who are beneficiaries of government health insurance. Individual data are captured in several different administrative databases, which can be linked through an encrypted health services number unique to each resident. The databases include the *Person Health Registration System (PHRS)*, the *Vital Statistics Registry* (VS), the *Prescription Drug Database* (PDP), the *Hospital Discharge Abstract Database* (DAD), and the *Medical Services Database* (MSB), among others (107).

The PHRS includes all residents eligible for Saskatchewan Health benefits. This includes over 99% of the population, with the only exceptions being individuals whose healthcare is entirely funded by the federal government (i.e., federal inmates, military personnel, and RCMP) (107). This database contains basic demographic information including patient sex and date of birth. It is also updated daily for changes in beneficiary status, such as termination due to death or emigration from the province (108). This file can be linked to Canadian Census data to estimate income quintile as well as location of residence (rural or urban) (109). The VS captures information on all births and deaths in the province. These records include the date of death and the cause of death coded by ICD-10 (107).

The PDP captures outpatient prescription claims for medications listed in the Saskatchewan drug formulary. Although the formulary covers an extensive list of prescription medications, it does not capture inpatient drug use, most non-prescription drugs, or professional samples (107). Also, approximately 9% of the population is ineligible for Drug Plan benefits because their prescription costs are paid by another government agency (primarily Registered Indians) (107,108). For each dispensation, information is collected on the patient, prescriber, drug, and cost. Drug information includes the drug name, strength, dosage form, dispensing date, and the quantity dispensed (108). However, it does not include information on the indication for use, the directions for use, or the days' supply (107).

The DAD captures information on every acute care inpatient separation (defined as discharge, transfer, or death as an inpatient) and day surgery for Saskatchewan beneficiaries,

including any hospitalizations that occur out-of-province (107). Emergency room visits are not captured in this database. Records include the date of admission and discharge, the specialty of the attending physician, up to 25 diagnoses from that visit coded based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD-10-CA), and up to 20 procedures performed during the hospital stay coded based on the Canadian Classification of Health Interventions (CCI) (108–110). The diagnosis recorded in the first position is considered the most responsible diagnosis for hospital admission (108,109). Prior to April 2001 diagnoses were recorded using the coding system of the International Classification of Disease, Ninth Revision (ICD-9), and the ICD-10-CA coding system was not fully adopted in the province until the 2002/03 fiscal year (109). Given that we are only considering ICD-10-CA codes in our extraction of hospital data (as will be discussed later), we will potentially be missing some relevant discharge diagnoses recorded by ICD-9 between January 1, 2002 and March 31, 2002.

The MSB captures claims for all insured physician services in the province. The data is primarily collected from claims submitted by physicians paid on a fee-for-service basis. Although salary-paid physicians are required to submit shadow or dummy billings, the consistency with which this is done is not known; consequently not all services are captured (107,108). As a result, the available diagnostic information is less complete compared to the DAD. Each medical claim includes an encrypted physician identifier, the date of service, the service (billing) codes, and a single three-digit ICD-9 diagnosis code from the visit (108). Also, the physician identifier can be linked to a separate file containing information on each physician's credentials/specialty and dates of registration. Given that not all of the available decimals of the ICD-9 codes are recorded, the diagnosis is also less specific than in the DAD. In addition, the data quality is questionable given that the diagnosis is only provided to support the claim for payment (107), and is not intended as a medical record for the patient.

3.2 Study Design

This was a population-based retrospective cohort study, created using linked administrative databases from the province of Saskatchewan, Canada.

3.3 Study Population

We captured all distinct treatment 'episodes' of VKA therapy among beneficiaries of the Saskatchewan Prescription Drug Plan between January 1, 2003 and December 31, 2010 (Figure 3.1). The index of a VKA treatment 'episode' was on the date of the first dispensation (i.e., fill) for a VKA following a washout period of at least 150 days where no fills for a VKA are recorded. A washout was used to attempt to capture a similar sample of subjects with new exposure to a VKA. The rationale for using a 150-day washout is based on the definition of the discontinuation of therapy, as described in the next section. The date of the first VKA dispensation that satisfied this criterion corresponded to the *index date* for that episode. Because VKA use can be episodic in nature, subjects may satisfy this inclusion criterion more than once; however, we only included the first occurring episode in our analyses. To enable the identification of baseline patient characteristics in the period leading up to the episode, based on administrative health data, VKA episodes were also excluded if the patient did not have continuous coverage through the Saskatchewan Provincial Drug Plan for at least 365 days prior to the index date.

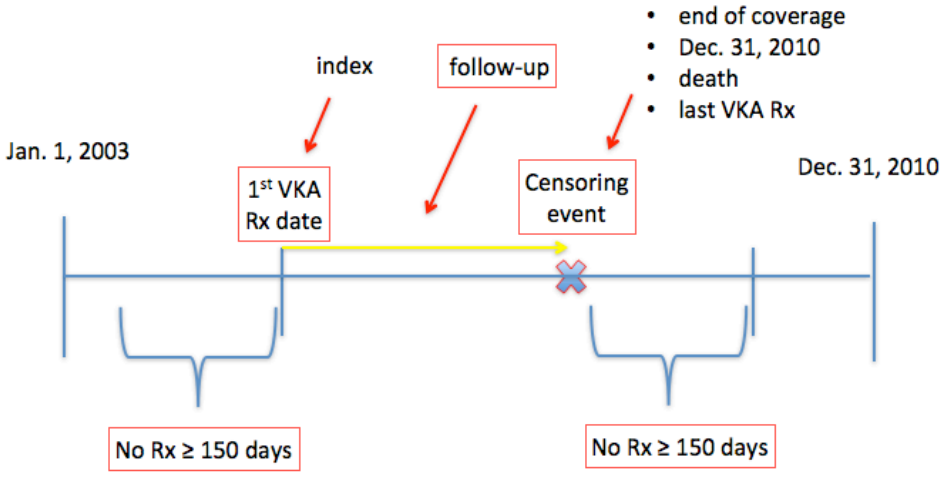

Figure 3.1 Identification of VKA Episodes and Duration of Follow-up

3.4 Objective 1 - INR Monitoring Patterns and Adherence to the 4-week Testing Interval

All eligible episodes of therapy were examined descriptively to determine the frequency of INR testing during VKA treatment. Frequency of INR testing was examined in a similar manner

as adherence to medications. Adherence was described overall and also divided into its two major sub-types: *non-persistence* versus *non-compliance* (defined later).

3.4.1 Patient Follow-up

Subjects were followed for the duration of continuous use of VKA therapy (Figure 3.1). Specifically, individuals were followed during the course of an episode of therapy defined from their first dispensation for a VKA (index date) until the earliest occurrence of any of the following events: discontinuation of the VKA, death, loss of beneficiary status, or the end of the observation period (Dec. 31, 2010). Discontinuation of therapy was defined as a gap between VKA dispensations of ≥ 150 days or a gap of ≥ 150 days between the last recorded dispensation and the end of available follow-up. This definition is based on the assumption that any single dispensation may supply up to 100 days of VKA medication in Saskatchewan; a 50% grace period has been added to assess for late refills (111). The discontinuation date corresponded to the last dispensation preceding the 150-day gap. This definition ensured that patients continued to receive their VKA therapy up until the estimated discontinuation date. Because some dispensations of a VKA may only last 34 days, a stricter definition of continuous VKA use was examined in a sensitivity analysis. Specifically, discontinuation of VKA therapy was established if a gap of ≥ 51 days was observed (i.e., rather than 150 days defined in the primary analysis). Using this definition, patients were less likely to have temporarily discontinued therapy (i.e., negating the need for INR monitoring), which could falsely decrease their measure of adherence to INR testing.

VKA episodes were excluded if only a single VKA fill was obtained or if no anticoagulant monitoring claims were recorded during the entire episode (8). Episodes were also excluded if the follow-up was ceased within 35 days of the beginning of therapy. This criterion was required to prevent immortal time bias among individuals with shorter periods of follow-up (112). Specifically, patients cannot mathematically satisfy the conditions for INR non-adherence (presented in the next section) if follow-up is shorter than 35 days. Therefore, these individuals would be 'immortal' to the endpoint of INR non-adherence (i.e., they would all exhibit 100% adherence).

3.4.2 Analysis of Adherence to INR Monitoring

Because a centralized laboratory information database was not yet ready for linkage (107), INR testing was estimated from the date of service for an anticoagulant monitoring claim (service code 763A) submitted by a physician to the MSB (113). Overall adherence to INR monitoring was calculated using a recognized formula for estimating adherence to medications, the *Continuous, Multiple-Interval Measure of Medication Gaps (CMG)*, as described by Steiner et al. (114,115). Specifically, we calculated intervals between consecutive INR testing dates, including the interval between the last INR test and the end of each patient's follow-up (Figure 3.2).

In the calculation of the CMG, the number of days between INR testing dates was compared against the recommended interval of 34 days (28 days plus a 20% grace period) (103). Given that the most recent anticoagulant guidelines suggested that a monitoring interval as long as 12 weeks is appropriate among stable VKA users (49), we also calculated adherence to an 84-day (i.e., 12-week) monitoring interval. Subsequently, the sum of the number of days exceeding each recommended interval represented the 'INR testing gap', as opposed to the 'medication gap' proposed by Steiner et al. (114). However, in contrast to the original CMG method, we did not allow for an accumulation of days covered in situations where the INR was tested at a greater frequency than the recommended 4-week interval. In doing so, frequent testing, especially at the start of therapy, was not applied to future gaps to falsely increase the adherence estimate.

Finally, the CMG for each episode was calculated by summing the total number of days in treatment gaps over the period of interest, and dividing it by the total number of days of observation in that period. Adherence was calculated by subtracting the CMG from 1.0 and converting the result into a percentage, where a value of 100% reflected complete adherence and 0% reflected complete non-adherence (116). Given that the CMG only considers the gaps in treatment, it was not possible to have greater than 100% adherence.

In addition to the overall mean adherence for each episode, we calculated adherence independently during the following time periods: 0-3 months, 4-6 months, 7-12 months, 13-24 months, and >24 months after the initiation of VKA therapy. In order to be eligible, subjects required continuous VKA use over the entire interval being evaluated.

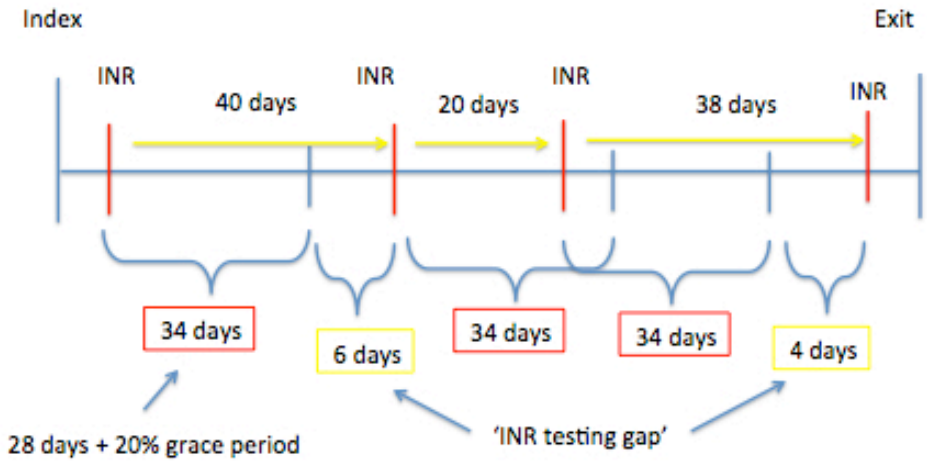

Figure 3.2 Measurement of Adherence with the CMG

3.4.3 Analysis of Persistence to INR Monitoring

Non-adherence to INR monitoring can occur as a result of infrequent testing (*non-compliance*) or from discontinuing INR monitoring altogether (*non-persistence*) (117). In order to evaluate the contribution of non-persistence to overall non-adherence to INR testing, we calculated the interval between the date of the last INR test over the observation period and the end of follow-up for each episode of VKA therapy (Figure 3.3). Any intervals greater than 34 days in length were assumed to be a result of non-persistence. In these instances, the date of discontinuation of INR monitoring was defined as 34 days after the last INR test, and the duration of non-persistence was calculated between the discontinuation date and the end of follow-up. Ultimately, we descriptively analyzed the proportion of non-adherence due to non-persistence to INR monitoring as well as quantified the duration of time that individuals continued their VKA treatment without INR testing.

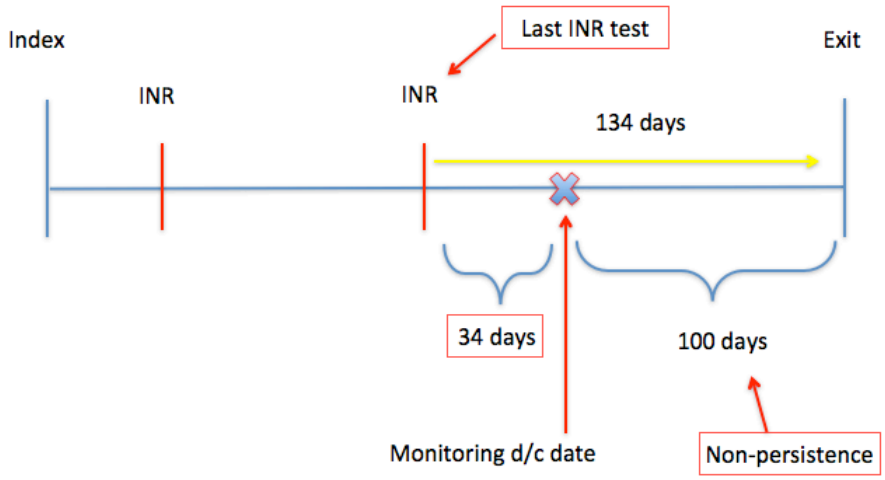

Figure 3.3 Measurement of Period of Non-persistence

3.5 Objective 2 - Predictors of Adherence to INR Monitoring

Once adherence was calculated for each episode of VKA therapy, we developed an explanatory model to test predictors of optimal monitoring using available data. Optimal INR monitoring was defined as ≥80% adherence calculated using the CMG. Although this cut-off was arbitrary, it is widely used to define optimal adherence to medications (100,102,118). Nevertheless, thresholds of 60% and 100% were tested in sensitivity analyses.

3.5.1 Patient Follow-up

Subjects were followed from their first dispensation for a VKA for each unique episode of therapy (index date) until the earliest occurrence of discontinuation of the VKA (as previously described), death, loss of beneficiary status, or the end of the observation period (Dec. 31, 2010). It was important to ensure that follow-up of patients was restricted to the period of VKA medication use only because INR testing is not necessary after the VKA is discontinued.

3.5.2 Covariates

We evaluated the significance of a number of different factors that may influence adherence to INR testing among patients receiving VKA medications. The specific factors were organized into three main groups: patient characteristics, physician-related factors, and factors specific to anticoagulation therapy. The specific factors and their rationale for testing are listed in Table 3.1. These variables were mostly selected from the literature based on their association

with adherence to warfarin and other cardiovascular medications. However, given the lack of literature pertaining specifically to the prediction of adherence to INR monitoring, additional variables were evaluated based on a plausible association with this outcome.

The specific indication for VKA therapy was also examined as a possible predictor of INR adherence. To do this, each episode of VKA therapy was assigned to one of the following diagnostic categories: atrial fibrillation (AF), treatment of venous thromboembolism (VTE), prevention of VTE following orthopedic surgery (VTEP), and prosthetic heart valves (PHV). Episodes that were associated with more than one of the previous indications, and those with an unidentified indication for VKA therapy, were grouped separately to ensure the categories were mutually exclusive (Table 3.2). Case definitions for each diagnosis were determined on or before the index date for each episode. In order to identify the most likely reason that VKA therapy was initiated, diagnoses or procedures were only considered if they were recorded within 30 days or 90 days prior to the first dispensation, depending on the indication being identified. Each indication is described as follows.

Atrial Fibrillation

An indication of AF was assigned to episodes with a hospital discharge diagnosis for AF (ICD-10-CA I48) in any position in the DAD record within 90 days prior to the index date. Alternatively, AF could be identified in the MSB, by a single claim with an ICD-9 diagnosis code of 427 within 90 days before the index date.

The 90-day screening window to identify outpatient dispensations following a hospital discharge diagnosis of AF was used in a large cohort study conducted in Denmark (119). The diagnostic coding of AF is from a validation study of hospital discharges from the Calgary health region. The ICD-10-CA code for AF included in any diagnostic position was found to have high sensitivity (98%) and specificity (96%) in a sample of patients diagnosed with stroke (120). However, given the association between AF and stroke, these estimates may not be representative of the general AF population.

The outpatient case definition of AF was based on an observational study in a commercially-insured cohort of AF patients in the United States. In order to identify the population with *chronic* AF, this study required that patients have two medical claims for AF

occurring at least six weeks apart (121). However, we chose to only require a single claim for AF. Reducing the required number of AF claims from two to one has been shown to improve sensitivity, while minimally impacting the specificity of an outpatient AF diagnosis (122). A study using medical claims data in Manitoba similarly demonstrated improved sensitivity with a reduction in the required number of claims with other cardiovascular diseases (123).

Treatment of Venous Thromboembolism

The indication of VTE was assigned to episodes with a hospital discharge ICD-10-CA code for PE (I26.0 to I26.9, O88.2) or DVT (I80.1 to I80.9, I82.1, I82.8, I82.9, O22.3, O22.9, O87.1) in any position in the DAD record, or a diagnosis of DVT (ICD-9 451 or 453) or PE (ICD-9 415) recorded in the MSB within 30 days prior to the index date.

The 30-day screening window to identify hospital discharges of VTE was used in an observational cohort study in the United States (75). However, because this study used codes from the 9th Revision of the International Classification of Diseases, specific ICD-10 codes were obtained from a different study that found a sensitivity of 89% and 58% for identifying hospitalized cases of PE and DVT, respectively. The authors suggested that the low sensitivity for capturing hospitalized cases of DVT was likely because the diagnosis is not included when it does not change the length of hospital stay or the care received when the patient is hospitalized (124). Given that the low sensitivity for capturing hospital diagnoses of DVT could limit the identification of episodes with this indication, the MSB was also screened in order to identify subjects managed by outpatient physicians.

The MSB was screened for ICD-9 codes derived from a study conducted with the medical service claims database in Quebec. This study determined that the sensitivity of claims for DVT was 87% in a 60-day window around the date of the diagnosis, and that the same estimate was 78% for PE. For our purposes, the limitation of these estimates is that the study population consisted of patients with a DVT, with or without a concurrent PE diagnosis (125). Consequently, the sensitivity of the PE diagnosis may not apply to isolated cases of PE. However, these events appear to be consistently captured using hospital discharge data as reviewed above. Another potential limitation was that the study by Tagalakis et al. examined 4-digit ICD-9 CM codes (125), whereas the Saskatchewan MSB only included 3 digits of the ICD-

9 coding system. As a result, it was expected that the corresponding 3-digit codes used in Saskatchewan might be less specific.

Prevention of Venous Thromboembolism

A VTEP indication was assigned to VKA episodes following a hospital discharge within the previous 30 days, that was associated with one of the following eligible VTEP diagnoses or procedures: procedure code for hip replacement (CCI 1.VA.53), knee replacement (CCI 1.VG.53), or hip fracture surgery (CCI 1.VA.53, 1.VA.74, 1.VC.74, and 1.SQ.53), or with a most responsible diagnosis for hip fracture (ICD-10-CA S72.0- S72.2).

These diagnostic and procedure codes were adopted from the Canadian Joint Replacement Registry (CJRR) (36) and the Canadian Institute for Health Information analysis of surgical wait times for hip fracture surgery (126).

Prosthetic Heart Valves

PHV surgery was assumed for those who were discharged from hospital in the 30 days prior to their index date with an associated procedure code for an intervention on the tricuspid valve (CCI 1.HS), the pulmonary valve (CCI 1.HT), the mitral valve (CCI 1.HU), or the aortic valve (CCI 1.HV)(110).

This definition was derived on the basis of clinical diagnoses and was reviewed by an experienced internal medicine specialist from the Saskatoon Health Region; however, to our knowledge it has never been formally validated. Valve position and type influence the risk of thromboembolism and duration of anticoagulation therapy (40). However, this definition is broad, and includes all codes for heart valve repair and replacement, with either bioprosthetic or mechanical valves. Furthermore, these include procedures done on the pulmonary and tricuspid valves, which are not explicitly discussed in the anticoagulation guidelines (19).

Multiple Indications and Unknown Indications

The episodes associated with more than one indication specified above were captured in the cohort with multiple indications. The episodes that did not satisfy any of the above criteria were categorized as “unknown indication”. This cohort was descriptively examined to determine if additional diagnoses should be added to the existing diagnostic categories (Table 3.2).

Table 3.1 Predictors of Adherence to be Tested

Variable	Definition	Rationale
Patient factors		
Age	Age in years at index date; tested as a continuous and categorical variable (binary variable – age <75 or ≥75 years old)	Clinically important and associated with improved adherence to a number of therapies (97–99) including INR testing (95,96)
Sex	Assigned female or male; dichotomous variable	Clinically important and male sex has been associated with better adherence to warfarin (101) and other drug therapies (97,99,100)
Urban or rural residence	Subjects residing in a census metropolitan area (Saskatoon or Regina) or in a census agglomeration (Estevan, Lloydminster, Moose Jaw, North Battleford, Prince Albert, Swift Current, or Yorkton) (127) were considered an urban resident. All other subjects were considered rural residents. Status determined at index year; dichotomous variable	Possible differences in access to INR testing and healthcare providers (104,105)
Income	Income quintile at index year, where Q1 is lowest and Q5 is highest income (109). Determined from the average household income in the subject's dissemination area defined by Statistics Canada; categorical variable	Measure of socioeconomic status – higher income has been associated with adherence to statin (100) and antihypertensive (97) drug therapies
Physician visits in prior year	Number of outpatient visits in the year prior to the index date; tested as a continuous variable and categorized into quintiles (0 to 11, 12 to 18, 19 to 25, 26 to 36, ≥37)	Measure of health services utilization at baseline associated with adherence to statin medications (98,103)
Hospitalizations in prior year	Number of hospitalizations (with an overnight stay – to exclude day surgeries) in the year prior to the index date; tested as a continuous and	Measure of comorbidity and health services utilization, associated with worse adherence to warfarin (101) and statin therapies (99,102)

Variable	Definition	Rationale
	categorical variable (0, 1, 2, ≥3).	
Charlson index	Charlson index (128) based on diagnoses in the DAD and MSB in the year prior to the index date; tested as a continuous and categorical variable (0, 1, 2, ≥3).	Measure of comorbidity - poor health has been associated with worse adherence to warfarin therapy (101,129) and other drug therapies (97)
Distinct diagnoses in prior year	Number of different diagnoses recorded to the third digit in ICD-9 and ICD-10-CA, from the DAD and MSB (109), within 365 days prior the index date; tested as a continuous variable and categorized into quartiles (0 to 6, 7 to 10, 11 to 16, and ≥17).	Measure of comorbidity - poor health has been associated with worse adherence to warfarin therapy (101,129) and other drug therapies (97)
Diabetes	≥ 2 claims in the MSB with ICD-9 code 250 or ≥ 1 discharge in the DAD with ICD-10-CA code E10 to E14 in any diagnostic position or ≥ 1 prescription drug claim for an oral diabetic agent or insulin (see Appendix) within 365 days prior to the index date (130); dichotomous variable	Associated with adherence to statin medications (98,100,103)
Stroke or transient ischemic attack (TIA)	Diagnosis in previous 365 days; identified by a primary hospital discharge with an ICD-10-CA code of either: I60 (excl. 160.8), I61, I63 (excl. I63.6), I64, H34.1, G45 (excl. G45.4), H34.0 (131).	Associated with adherence to anticoagulation (96) and statin therapies (99,102)
Number of CV medications	Number of distinct cardiovascular (CV) drugs with at least one dispensation within 180 days prior to the index date. This included the following medication classes (97) from the Saskatchewan Drug Formulary (132)(see Appendix): antihypertensive	Associated with adherence to statin medications (97,98,100)

Variable	Definition	Rationale
	agents (diuretics, β blocker, RAAS agent, CCB), statins, other lipid agents, cardiac agents, anticoagulants, antiplatelets, insulin, oral diabetes agents; tested as a continuous and categorical variable (0, 1, 2, 3, ≥4)	
Number of non-CV medications	Number of distinct non-cardiovascular drugs with at least one dispensation within 180 days prior to the index date. This included the following medication classes (97) from the Saskatchewan Drug Formulary (132)(see Appendix): antidepressants, antipsychotics, glucocorticosteroids (oral, inhaled, parenteral), bisphosphonates, hormone replacement therapy, uric acid agents, migraine agents, NSAIDs, proton pump inhibitors, H2-receptor antagonists, misoprostol, other gastrointestinal agents, transplant agents; tested as a continuous and categorical variable (0, 1, 2, ≥3)	Associated with non-adherence to statin medications (97,98,100)
Physician factors		
Practitioner type (specialist, general practitioner)	Type of practitioner submitting the greatest number of claims for monitoring anticoagulation (service code 763A)(113) over follow-up; as a categorical variable	Possible differences in experience monitoring anticoagulation
Anticoagulation therapy factors		
Indication for anticoagulation	Assigned by cohort definitions found in Table 3.2, into *AF, VTE, VTEP, PHV, multiple indications,* or *other indication for use*; as a categorical variable	Possible differences in comorbidity, duration of VKA therapy, and how aggressively the patient is treated

Variable	Definition	Rationale
Duration of VKA therapy	Number of days between index and exit dates, stratified into the following categories: 0 to 1, 2 to 3, 4 to 6, 7 to 12, 12 to 24, and >24 months	Possibility of consistently high adherence in the early phase after beginning a VKA episode
New vs. repeat VKA use	Episodes meeting a 1-year washout were classified as *new use*, and all others as *repeat use* (only meeting the 150-day washout); as a dichotomous variable	Prior warfarin use has been associated with poor adherence to taking the medication (101,129)
Index year	The year of starting VKA therapy; categorized as 2003-04, 2005-06, 2007-08, 2009-10.	First-fill discontinuation of statins (102) and antihypertensives (97) decreased over time

Table 3.2 Case Definitions of Indications for VKA Therapy

Data Source	Diagnostic Code	Time Frame	References
Atrial Fibrillation (AF)*			
MSB	ICD-9 427	Within 90 days before (and including) index date	Sarawate 2006 (121)
DAD	ICD-10 CA I48 (*any position – primary or secondary*)	Within 90 days before (and including) index date	Hansen 2008 (119); Kokotailo 2005 (120)
Active Venous Thromboembolism (VTE)*			
MSB	ICD-9 451 453 415	Within 30 days before (and including) index	Tagalakis 2011 (125)
DAD	ICD-10 CA I26.0 to I26.9	Within 30 days before (and including) index date	Casez 2010 (124);

	I80.1 to I80.9, I82.1, I82.8, I82.9, O88.2, O22.3, O22.9, O87.1 (*any position – primary or secondary*)		Willey 2004 (75)
Prevention of Venous Thromboembolism/ Orthopedic Surgery (VTEP)			
DAD	Procedure (CCI) 1.VA.53 1.VG.53 1.VA.53, 1.VA.74, 1.VC.74, and 1.SQ.53 ICD-10 CA S72.0- S72.2 *(primary position only)*	Within 30 days before (and including) index date	CIHI CJRR annual report 2009 (36); CIHI hip fracture wait times 2011 (126)
Prosthetic Heart Valves (PHV)			
DAD	Procedure (CCI) 1.HS 1.HT 1.HU 1.HV	Within 30 days before (and including) index date	No reference found – Codes pulled on inspection. Reviewed by a content expert**

* Diagnosis can be confirmed with records from either the MSB or DAD

** Content expert: Dr. Thomas Wilson, MD, FRCPC

3.5.3 Statistical Analysis

Multiple logistic regression models were built using optimal INR adherence as the dependent variable (sensitivity analyses were carried out to evaluate modifications to the 80% threshold).

Prior to model development, each variable was described. The most appropriate form of each variable was explored with a plot of the deciles of the predictor variable against its

regression coefficient. A continuous variable was used when this plot formed a reasonably straight line. All other variables were categorized based on clinical relevance or their distribution.

We then examined correlations between the following variables, using Spearman's rank-order correlation coefficient: the comorbidity measures (Charlson index, distinct diagnoses, physician visits, hospitalizations, diabetes, stroke, CV and non-CV medications), duration of VKA therapy and indication, urban/rural and prior hospital/physician visits, income and comorbidity/drug use. Where variables were found to be highly correlated (i.e., $r > 0.5$), we measured the *variance inflation factor* (VIF). Collinearity was assumed if the VIF was greater than 10 (133), in which case the preferred variable was chosen based on model fit.

Given that individual physicians may provide anticoagulant services to several different patients, there was the potential for a clustering effect by physician. To investigate the patient-level and physician-level characteristics associated with adherence to INR monitoring, we conducted hierarchical (random effects) logistic regression analyses. Individual physician identification was considered a random effect in these models.

First, we fit a null model only containing the physician variable as a random intercept to test if the clustering effect by physician was important in the model. The *intraclass correlation coefficient* (ICC) was used to quantify the clustering effect, and was calculated as follows: $ICC = V_A/(V_A + 3.29)$, where V_A is defined as the area level variance (134). In order to determine if a minimum cluster size was required, we compared the ICC to models restricted to clusters with at least 3 patients and with at least 5 patients.

Next, a hierarchical logistic regression model was developed using an empiric approach to variable selection. The purpose of this method was to identify the variables that were independently and strongly associated with adherence to INR testing. To select variables to include in the model, we fit a full model that included all available covariates. From this, a reduced model was created by excluding all variables with a p-value > 0.05 for the Wald statistic in the full model. We then removed one variable at a time from the reduced model, and used a partial *likelihood ratio test* (LRT) to confirm its significance in the model (135) at a nominal level of significance of $\alpha = 0.05$.

Once the important covariates had been identified, the variables that were originally excluded from the full model were added back to the model one at a time to test for confounding and for significance in the model. To assess confounding, we compared the estimated coefficients in the reduced model and the full model. Any coefficient demonstrating a considerable change in magnitude (ex. > 20%) suggested that the excluded variable was required in the model as a confounder (135).

Subsequently, we explored specific pairs of variables for interactions. Poor access to healthcare providers in rural communities (104,105) could affect the adherence of the older, sicker, and lower income subjects especially. Given this, we explored the interaction of urban or rural residence with age, comorbidity, and income. We also explored an interaction between indication and age, given that there are likely fundamental differences in how anticoagulants are prescribed for the different age groups (136–138). Given the fear of bleeding, practitioners might only select anticoagulants for their healthier and motivated elderly patients.

We assessed the significance of adding one interaction term at a time to the main effects model using the LRT (135). All variables remaining in the model were considered independent predictors of adherence to INR monitoring.

A sensitivity analysis of the definition of optimal adherence (≥ 80%) was performed on the full model, using a 60% and 100% adherence threshold. Consideration was given to whether the resulting odds ratios changed the clinical interpretation of each individual variable.

All analyses were conducted using PROC GLIMMIX on SAS® software, Version 9.3 (139).

4 RESULTS

4.1 Indications for New Episodes of VKA Therapy

Between January 1, 2002 and December 31, 2010 there were 1,352,436 dispensations for a VKA in Saskatchewan. Of these, we identified 44,467 new episodes of VKA therapy among 35,167 unique individuals (Figure 4.1). The most common indication for a new episode of anticoagulation was AF (34%)(Table 4.1). The majority of AF cases (51%) were identified in the MSB only, while 34% were found in both the MSB and the DAD. There were 2,553 episodes (6%) that satisfied criteria for more than one indication. Again, AF was the most common condition among this subgroup (n=1,833; 69%).

There were 12,921 episodes (29%) that did not meet any of the diagnostic definitions previously defined. Upon review, no predominant diagnosis emerged frequently. Thirty-three percent (4204/12921) of these cases were discharged from hospital in the 30 days preceding the index VKA. However, manual review of all primary diagnosis codes in the DAD did not reveal any consistent diseases or conditions. Similarly, 91% (n=11,820) of episodes were preceded by at least one physician visit within 30 days prior to beginning VKA therapy, but manual review of ICD codes in the MSB did not reveal any common diagnoses. Finally, we expanded the criteria for an AF diagnosis to include records up to 365 days prior to the index date. This sensitivity analysis identified 2,504 additional AF cases, which only accounted for 19% of all episodes in the 'other' cohort.

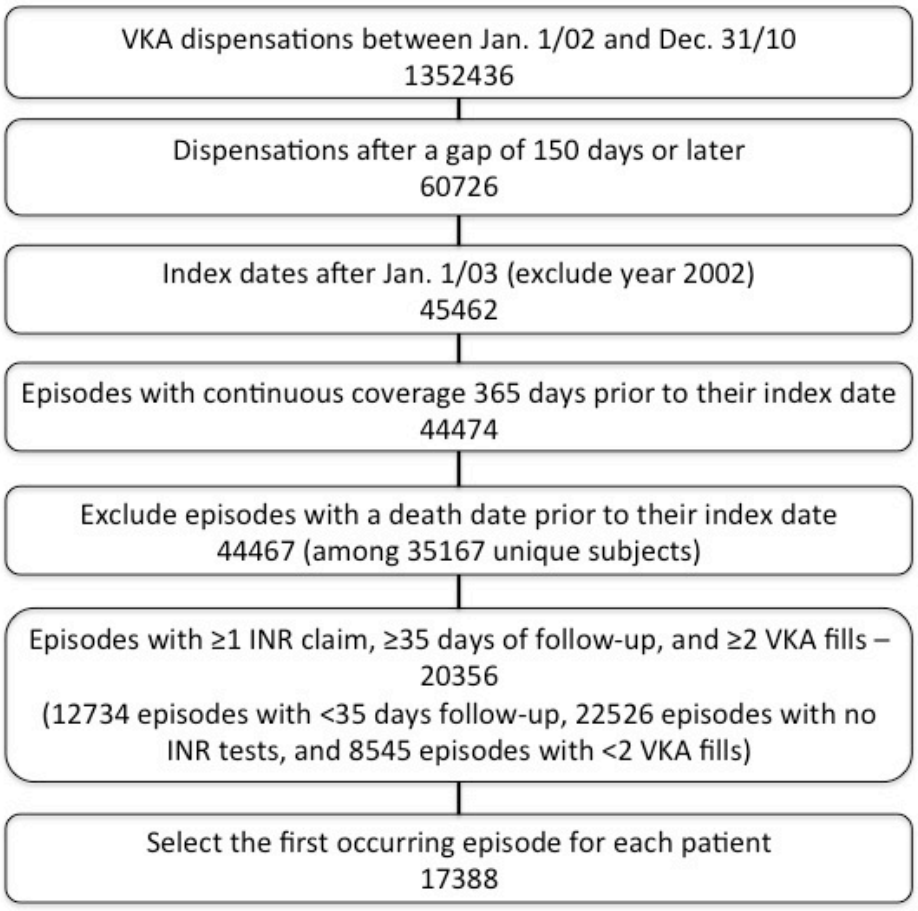

Figure 4.1 Flow Diagram of Episode Selection

Table 4.1 VKA Episodes in Each Disease Cohort

Cohort	Frequency*	Percent*
Atrial fibrillation (AF)	15145	34.06
Venous thromboembolism (VTE)	6422	14.44
Prevention of venous thromboembolism (VTEP)	6625	14.80
Prosthetic heart valve (PHV)	801	1.80
Multiple indications	2553	5.74
Other (unknown) indication	12921	29.06

** Corresponds to number of episodes of VKA therapy, not subjects*

4.2 Adherence Cohort

From the 44,467 new episodes, we excluded subjects with < 35 days follow-up (n=12,734), no anticoagulant monitoring claims on record (n=22,526), or with fewer than 2 dispensations for a VKA (n=8,545). Ultimately there were 17,388 subjects that were eligible for the adherence analysis (Figure 4.1). Mean age at index was 70.2 years, 52.0% were male, and 57.7% resided in urban areas (Table 4.2). Patients in the AF and VTEP cohorts were older on average (74.4 and 76.5 years respectively) compared to individuals categorized with other diagnoses. Also, fewer males were observed in the VTEP cohort (27.5%) compared to the other indications. The total number of episodes with a missing value for residence and income was very small (0.7% and 0.8% respectively).

The frequency of physician visits and hospitalizations in the year prior to index was highest among the subjects with multiple indications for VKA therapy. Comorbidity, as measured by the Charlson index and the number of distinct diagnoses, was also highest in the cohort with multiple indications. Prior stroke or TIA, which can be an important indication for VKA therapy in some patients, was observed in 5.7%, and was higher in the cohort with AF and an unknown indication (6.7% and 8.7% respectively). The total number of distinct cardiovascular medications filled within 180 days prior to the index date was highest in the AF and PHV cohorts, while essentially the opposite was true of the number of non-cardiovascular medications.

Virtually all episodes of VKA therapy (99%) were monitored by a general practitioner regardless of diagnostic category. Also, the majority of new episodes (87.0%) were undertaken by patients with no VKA fills in the previous year, while the remaining 13.0% of patients received at least one VKA fill between 151 days and 365 days prior to the index date. The percentage of individuals receiving VKAs for the various diagnostic indications was similar throughout the study period with the exception of the VTEP cohort, where the proportion of new VKA starts declined substantially over time (34.4% in 2003-2004 and 6.3% in 2009-2010). This observation was expected given the national trend of replacing warfarin with low-molecular weight heparins over a similar time period (36).

Characteristics of subjects who were excluded from the adherence analysis were very similar to the study population with a few exceptions. Missing data for physician credentials

occurred in only 0.6% of the eligible episodes compared to 69.4% of the ineligible episodes. This high proportion can be explained given that 51% of episodes were excluded because they had no INR monitoring claim, and therefore no physician could be identified at all. Lastly, the excluded subgroup had a higher percentage of repeat VKA episodes due to the inclusion of only a single episode per patient.

Table 4.2 Patient Characteristics

Baseline Characteristic	Eligible Subgroup[a]							Ineligible Subgroup (N= 27079)
	AF (N= 7746)	VTE (N= 3238)	VTEP (N= 512)	PHV (N= 442)	Multiple (N= 1020)	Other (N= 4430)	All (N= 17388)	
Age[c], mean	74.37	62.08	76.53	62.17	71.71	68.46	70.18	69.872
Male sex[c] , %	53.30	46.79	27.54	65.38	49.51	55.69	52.02	50.02
Urban, %	55.06	61.86	58.59	53.85	59.12	59.19	57.69	57.47
(% missing)	(0.50)	(0.86)	([b])	([b])	([b])	(0.81)	(0.65)	(0.70)
Income quintile[c]. %								
1st	18.91	17.88	21.48	[b]	19.71	17.77	18.38	19.56
2nd	21.21	21.65	17.19	21.95	22.06	21.92	21.42	20.10
3rd	23.73	23.69	24.41	24.66	21.47	24.38	23.80	23.07
4th	19.60	18.62	18.36	22.85	19.12	18.78	19.23	18.99
5th	15.85	17.23	18.55	17.65	16.67	16.39	16.42	17.33
Missing	0.70	0.93	0.00	[b]	0.98	0.77	0.75	0.94
Physician visits[c], %								
0 to 13	24.50	27.73	9.38	[b]	4.51	26.91	23.49	20.57
14 to 19	20.01	17.82	18.75	[b]	12.16	19.32	18.49	19.26
20 to 26	19.30	17.91	26.37	18.33	16.76	19.44	19.11	20.11
27 to 37	19.43	17.23	22.27	42.76	28.43	16.93	19.59	20.16
≥38	16.76	19.30	23.24	35.75	38.14	17.40	19.32	19.90
Hospitalizations [c], %								
0	35.31	25.32	0.00[d]	0.00[d]	3.73	47.27	32.71	31.29
1	39.44	42.22	52.93	66.29	45.78	30.65	39.17	39.69
2	14.81	18.31	27.54	21.49	28.73	12.84	16.32	16.40
≥3	10.44	14.14	19.53	12.22	21.76	9.23	11.80	12.61
Charlson Index[c], %								
0	37.17	48.98	42.38	25.34	29.02	34.00	37.93	43.74
1	27.36	19.73	27.73	32.58	27.16	26.39	25.82	23.50
2	16.67	13.40	15.23	20.59	17.35	[b]	[b]	14.25
≥3	18.81	17.88	14.65	21.49	26.47	22.89	20.07	18.42
Missing	0.00	0.00	0.00	0.00	0.00	[b]	[b]	0.09
Distinct diagnoses [c], %								
0 to 6	23.04	22.88	9.18	2.94	3.14	28.89	22.42	24.14
7 to 10	25.10	23.41	22.85	18.33	11.57	25.03	23.73	24.87
11 to 16	27.18	25.91	32.42	34.84	30.39	24.88	26.89	26.13
≥17	24.68	27.79	35.55	43.89	54.90	21.20	26.96	24.86

Baseline Characteristic	Eligible Subgroup[a]							Ineligible Subgroup (N= 27079)
	AF (N= 7746)	VTE (N= 3238)	VTEP (N= 512)	PHV (N= 442)	Multiple (N= 1020)	Other (N= 4430)	All (N= 17388)	
Diabetes, %	20.69	13.65	19.14	18.10	17.55	21.24	19.23	18.56
Stroke/TIA[c], %	6.66	1.67	[b]	[b]	2.16	8.71	5.67	2.65
Number of distinct cardiovascular drugs dispensed within 180 days prior to the index date^, %								
0	3.78	41.17	20.70	2.04	11.27	15.53	14.63	20.39
1	11.17	17.70	20.51	10.86	13.33	13.93	13.48	15.69
2	15.31	14.14	19.14	13.57	16.08	14.54	15.01	15.68
3	17.87	9.11	14.06	14.71	14.71	13.81	14.83	14.28
4	16.34	7.32	9.77	18.33	12.65	13.70	13.63	11.89
≥5	35.53	10.56	15.82	40.50	31.96	28.49	28.42	22.07
Number of distinct non-cardiovascular drugs dispensed within 180 days prior to the index date[c], %								
0	48.04	43.76	27.93	55.66	39.90	46.28	45.92	42.42
1	28.75	27.61	27.54	26.02	29.80	28.31	28.38	28.64
2	13.99	15.04	23.83	11.09	17.25	14.81	14.80	16.13
≥3	9.22	13.59	20.70	7.24	13.04	10.61	10.90	12.81
Type of practitioner[e] with the most INR claims[c], %								
GP	99.14	98.46	>95[b]	100.00	99.22	99.07	99.02	30.49
Specialist	0.19	1.05	[b]	0.00	[b]	0.18	0.33	0.08
Missing	0.67	0.49	[b]	0.00	[b]	0.74	0.64	69.43
New VKA use[c], %	87.89	95.52	96.29	>95[b]	96.37	74.92	87.03	73.86
Index year[c], %								
2003-2004	27.58	26.44	34.38	24.21	25.29	29.16	27.75	24.03
2005-2006	26.04	26.04	33.40	23.76	29.12	25.49	26.26	25.05
2007-2008	24.81	25.29	25.98	25.11	23.63	23.32	24.49	25.63
2009-2010	21.57	22.11	6.25	26.92	21.96	22.03	21.50	25.29
Follow-up, %								
0-34 days	0.00	0.00	0.00	0.00	0.00	0.00	0.00	47.03
35-90 days	6.57	10.07	44.14	36.43	20.59	9.37	10.62	11.44
91-180 days	9.01	22.98	21.09	9.95	17.75	14.31	13.85	11.75
181-365 days	14.48	24.18	13.48	8.82	17.06	17.52	17.04	10.60
366-730 days	18.86	16.46	10.16	11.31	15.00	19.01	17.78	8.71
≥731 days	51.07	26.31	11.13	33.48	29.61	39.80	40.71	10.47

[a] Episodes with ≥1 INR claim, ≥35 days of follow-up, and ≥2 VKA fills

[b] Corresponds to a cell size ≤5

[c] Significant p-value (≤0.05) for comparison of eligible and ineligible groups. Significance was determined using a t-test for continuous variables and a chi-square test for categorical variables

[d] Expected that all subjects have at least one hospitalization, given that the case definition only included hospital diagnoses

[e] Adherence calculations included all INR monitoring claims (regardless of physician identification or type)

4.3 Follow-up

The overall mean duration of follow-up was 797.2 (SD 747.5; median 514.0) days using a 150-day gap to define the discontinuation of VKA therapy (Table 4.3). The longest duration of follow-up was observed in the AF cohort (mean 952.1, SD 765.4; median 755.0 days), while the VTEP cohort had the shortest duration of therapy (mean 306.7, SD 487.9; median 107.5 days). This difference is expected because VKA therapy for VTEP is often only used short-term following surgical procedures. The most common reason for study exit was discontinuation of VKA therapy (42%). Sensitivity analysis on the definition of VKA discontinuation influenced overall follow-up time significantly. When using a 51-day gap to define discontinuation, the mean duration was shortened to 303.1 (SD 378.3; median 158.0) days (Table 4.3). By restricting follow-up to periods with no more than 51 days between VKA dispensations, it is less likely that temporary breaks in VKA therapy were unintentionally captured; thus, leading to misclassification of INR non-adherence.

Table 4.3 Follow-up Using 150-day and 51-day Gaps to Define VKA Discontinuation

Gap	Mean	Std. Dev.	25th Percentile	Median	75th Percentile	Minimum	Maximum
150-day	797.15	747.46	184.00	514.00	1258.00	35.00	>2915**
51-day	303.05	378.34	77.00	158.00	360.00	35.00	>2756**

** Corresponds to a cell size ≤5

4.4 Objective 1 - INR Monitoring Patterns and Adherence to the 4-week Testing Interval

4.4.1 Adherence

The median interval to the first INR claim date was 26 days following the first fill of a VKA, with a maximum interval greater than 2,618 days (Table 4.4). Median adherence to INR testing corresponding to a recommended interval of four weeks was 74.4% (Table 4.5). Median adherence was highest in the VTEP and PHV cohorts (90.5% and 88.4% respectively), and lowest in the AF and 'other' cohort (70.9% and 71.6% respectively). Among all patients in the study, the percentage exhibiting optimal adherence was 44.3% (Table 4.6).

Important differences in the estimates of INR adherence were observed in sensitivity analyses. When the acceptable duration between INR tests was expanded to 12 weeks (i.e., 84 days) rather than 4 weeks, median adherence increased to 97.8% (Table 4.5). Also, when patient

follow-up was limited to episodes of continuous VKA therapy with no intervals between medication dispensations greater than 51 days, median adherence increased to 90.0% (Table 4.7). This result was expected given that the 150-day gap (i.e., used in the primary analysis) is more likely to inadvertently include periods during which the patient temporarily discontinued therapy and did not require monitoring.

Overall there was a consistent pattern of decreasing adherence over the course of therapy (Table 4.8). Compared to the overall median value (74.4%), adherence was higher in the intervals between the index date and 90 days (85.6%) and between 90 and 180 days (80.0%), but decreased to as low as 61.7% beyond two years of therapy.

Table 4.4 Interval Between the Index Date and the First INR Test Date

Mean	Std. Dev.	25th Percentile	Median	75th Percentile	Minimum	Maximum
121.33	289.40	13.00	26.00	64.00	0.00	>2618**

** Corresponds to a cell size ≤5

Table 4.5 Descriptive Statistics of Adherence Measured Using a 4 and 12-week Interval for Testing

Interval	Mean	Std. Dev.	25th Percentile	Median	75th Percentile	Minimum	Maximum
34-day	66.35	30.81	41.05	74.42	95.19	<2**	100.00
84-day	80.27	27.76	65.41	97.82	100.00	<5**	100.00

** Corresponds to a cell size ≤5

Table 4.6 Proportion of the Cohort who met 60%, 80%, and 100% Adherence Thresholds Using a 4-week Interval for Testing

	Frequency	Percent
≥60% adherence	10889	62.62
≥80% adherence	7697	44.27
100% adherence	3127	17.98

Table 4.7 Descriptive Statistics for Adherence Using a 51 and 150-day Gap to Define VKA Discontinuation

Gap	Mean	Std. Dev.	25th Percentile	Median	75th Percentile	Minimum	Maximum
51-day	77.83	27.17	62.50	89.96	100.00	<4**	100.00
150-day	66.35	30.81	41.05	74.42	95.19	<2**	100.00

** Corresponds to a cell size ≤5

Table 4.8 Descriptive Statistics for Adherence at Intervals After Index Date Using a 4-week Interval for Testing

Days	Mean	Std. Dev.	25th Percentile	Median	75th Percentile	Minimum	Maximum
0-90	66.72	40.00	42.22	85.56	100.00	0.00	100.00
90-180	62.38	42.51	0.00	80.00	100.00	0.00	100.00
180-365	58.62	39.21	20.54	70.81	98.92	0.00	100.00
365-730	55.36	37.53	18.63	63.56	92.33	0.00	100.00
≥730	54.96	36.39	18.18	61.66	89.96	0.00	100.00

4.4.2 Persistence

Non-adherence with INR testing can result from long delays between INR tests (i.e., poor execution) or complete discontinuation of testing altogether (i.e., non-persistence). Non-persistence accounted for a relatively small percentage of overall non-adherence to INR testing (mean 22.8%; median 0%)(Table 4.9). Similarly, the median duration of non-persistence among non-adherent episodes was low also (0 days)(Table 4.10). Persistence was similar in the various disease cohorts, and had very little impact on the adherence measurement in all cases.

Table 4.9 Persistence Among Episodes with Gaps in Testing - Percentage of Total Gaps Contributed by the Last Gap

Mean	Std. Dev.	25th Percentile	Median	75th Percentile	Minimum	Maximum
22.75	35.26	0.00	0.00	36.89	0.00	100.00

Table 4.10 Duration of Non-persistence (Days)

Mean	Std. Dev.	25th Percentile	Median	75th Percentile	Minimum	Maximum
90.95	262.11	0.00	0.00	39.00	0.00	>2396**

** Corresponds to a cell size ≤5

4.5 Objective 2 - Predictors of Adherence to INR Monitoring

4.5.1 Testing for the Clustering Effect by Physician

Altogether, there were 898 physicians monitoring patients in the cohort and 50% of physicians were monitoring at least 10 patients in the study (Table 4.11). Three hundred-thirty physicians (36.8%) followed 5 or fewer patients. Because small clusters contribute little to no variability, it was necessary to determine if restricting the cluster size provided an important change to the *intraclass correlation coefficient* (ICC). A null model including all subjects and cluster sizes resulted in an ICC of 0.34. There was no change to the ICC when the cluster size was restricted to a minimum of 3 and 5 subjects. Finally, restricting the cluster size to a minimum of 50 patients (resulting in 101 clusters) as has been suggested in the literature (140), resulted in an ICC of 0.27. Due to the minimal change of the ICC, it was felt it would be appropriate to include all subjects and cluster sizes for further analysis. Furthermore, given the relatively high value of the ICC (0.34), the random physician effect is required in the model to control for clustering.

Table 4.11 Distribution of Physician Cluster Sizes

Mean	Std. Dev.	Minimum	Median	Maximum
19.26	22.85	1.00	10.00	138.00

4.5.2 Model Building

The Wald test statistics for all available covariates in the full model are found in Table 4.12. The variables that had the largest effect on the model fit were rural or urban residence ($p<0.001$) and the duration of follow-up ($p<0.001$). All of the variables with a significant Wald test statistic ($p \leq 0.05$) in the full model were also found to be significant individually and were retained. Although age was not statistically significant, it was ultimately kept in the model for clinical interest and to control for possible confounding. Income quintile ($p<0.001$) and practitioner specialty ($p<0.001$) substantially improved the model fit when added back to the model, and were kept for further analysis. Although the number of diagnoses and CV drugs both modified parameter estimates by approximately 20%, the changes to their respective odds ratios

were very small (approximately 2% to 5%). It was for this reason that these variables were ultimately deleted, along with any of the remaining variables.

Once all the important predictors in the model were identified, each of the pre-specified interactions was tested in the model. The interaction of urban or rural residence with both income ($p=0.10$) and comorbidity ($p<0.90$) were not significant at $\alpha = 0.05$. However, there was a statistically significant interaction between age and indication ($p<0.025$) and also between age and rural or urban residence ($p=0.025$).

Table 4.12 Test Statistics of Full Model, Including All Variables

Effect	Num DF	Den DF	F Value	Pr > F
Age	1	16121	1.10	0.2935
Sex	1	16121	7.51	0.0062
Urban/Rural	1	16121	67.97	<.0001
Income quintile	4	16121	1.10	0.3525
Physician visits	4	16121	5.79	0.0001
Hospitalizations	3	16121	4.78	0.0025
Charlson index	3	16121	3.31	0.0191
Distinct diagnoses	3	16121	2.32	0.0731
Prior diabetes	1	16121	5.08	0.0242
Prior stroke	1	16121	2.47	0.1162
CV drugs	4	16121	0.98	0.4159
Non-CV drugs	3	16121	4.91	0.0021
Practitioner type	1	16121	3.10	0.0783
Indication	5	16121	6.33	<.0001
Duration of follow-up	4	16121	366.05	<.0001
New VKA use	1	16121	11.29	0.0008
Index year	3	16121	4.06	0.0068

4.5.3 Odds of Optimal Adherence

The odds of achieving optimal adherence to INR monitoring for variables in the empiric multivariable model are reported in Table 4.13. Variables associated with increased odds of

adherence to INR monitoring were female sex, a greater number of prior physician visits, and a recent index year. Of these, the number of physician visits in the prior year was the strongest predictor (12-18 visits OR 1.15, 95% CI 1.01-1.30; ≥37 visits OR 1.51, 95% CI 1.28-1.77). The odds of adherence were decreased by the number of prior hospitalizations and a longer duration of follow-up. Compared to subjects with 1 to 3 months of follow-up, the OR of optimal adherence was 0.16 (95% CI 0.13-0.20) with 3 to 6 months of follow-up and 0.04 (95% CI 0.03-0.05) with greater than 2 years of follow-up. The small magnitude of these odds ratios reflects the high degree of adherence in the first 3 months of follow-up. The percentage of individuals with less than 3 months of follow-up achieving optimal adherence was 85% while the corresponding result was 30% for those with follow-up more than 2 years.

The remaining variables in the model only had modest predictive power, with odds ratios ranging between 0.8 and 1.2. The odds of adherence increased with female sex (OR 1.12, 95% CI 1.03-1.22) and a recent index year (OR 1.06 in 2005/06; OR 1.19 in 2009/10). However, subjects in the latest index years had the shortest duration of follow-up (mean follow-up 1148 days and 306 days in 2003/04 and 2009/10, respectively), so this result may be biased. Being a VKA user in the prior year decreased the likelihood of adherence (OR 0.81, 95% CI 0.71-0.92). Adherence also appeared to be worse among those taking 3 or more non-cardiovascular drugs (OR 0.77, 95% CI 0.67-0.88), and those with a greater extent of comorbidity (≥3 vs. 0 prior hospitalizations OR 0.70, 95% CI 0.59-0.83; Charlson index ≥3 vs. 0 OR 0.89, 95% CI 0.78-1.02).

Table 4.13 Odds Ratios (OR) of Optimal Adherence for Variables in the Empiric Model (Using 80% Adherence Threshold)

Effect	OR	95% CI
Age (<75 yrs.)	---	---
Sex (Female)	1.12	1.03-1.22
Rural	---	---
Income quintiles		
2 vs. 1	1.09	0.96-1.24
3 vs. 1	1.04	0.91-1.18
4 vs. 1	1.04	0.91-1.18
5 vs. 1	1.14	0.99-1.31
Physician visit		
12-18 vs. 0-11	1.15	1.01-1.30
19-25 vs. 0-11	1.29	1.13-1.48
26-36 vs. 0-11	1.29	1.12-1.49

Effect	OR	95% CI
≥37 vs. 0-11	1.51	1.28-1.77
Hospitalizations		
1 vs. 0	0.94	0.85-1.04
2 vs. 0	0.86	0.74-0.98
≥3 vs. 0	0.70	0.59-0.83
Charlson		
1 vs. 0	1.02	0.92-1.13
2 vs. 0	0.84	0.74-0.95
≥3 vs. 0	0.89	0.78-1.02
Prior diabetes		
No vs. Yes	1.11	1.00-1.22
Non-CV drugs		
1 vs. 0	0.93	0.85-1.02
2 vs. 0	0.99	0.88-1.11
≥3 vs. 0	0.77	0.67-0.88
Practitioner Type		
GP vs. SP	2.72	0.88-8.40
Indication		
Other vs. AF	---	---
Multi vs. AF	---	---
PHV vs. AF	---	---
VTEP vs. AF	---	---
VTE vs. AF	---	---
Follow-up (days)		
91-180 vs. 35-90	0.16	0.13-0.20
181-365 vs. 35-90	0.09	0.08-0.11
366-730 vs. 35-90	0.06	0.05-0.07
≥731 vs. 35-90	0.04	0.03-0.05
Recent vs. new VKA use	0.81	0.71-0.92
Index year		
2005-06 vs. 03-04	1.06	0.95-1.18
2007-08 vs. 03-04	1.20	1.07-1.34
2009-10 vs. 03-04	1.19	1.04-1.36

--- The variable is a part of an interaction term, for which the odds ratios are listed separately in Table 4.14.

4.5.4 Interactions

A significant interaction was identified between age and urban/rural residence; however, age did not appear to modify the impact of rural status in a meaningful way (Table 4.14). The odds of optimal adherence among individuals living in rural areas was decreased by 36.5% for individuals <75 years of age and by 44.8% for individuals ≥75. The strength of this association is also clinically meaningful, and suggests that rural residents may have poorer access to INR

monitoring overall.

Several other significant interactions were identified in the model (Table 4.14). However, most of the interactions did not appear to represent meaningful effect modification. The largest effect modification was observed between age and indication for VKA therapy (i.e., diagnosis). However, no consistent pattern could be identified with respect to this finding.

Table 4.14 Odds Ratios (OR) for the Interaction Terms in the Empiric Models

Variables held constant		Comparison	OR	95% CI
Age <75 yrs.	----------	Rural vs. Urban	0.64	0.55-0.73
Age ≥75 yrs.	----------	Rural vs. Urban	0.55	0.47-0.64
Urban	Other	Age <75 yrs. vs. ≥75 yrs.	0.83	0.71-0.98
Rural	Other	Age <75 yrs. vs. ≥75 yrs.	0.96	0.80-1.16
Urban	Multi	Age <75 yrs. vs. ≥75 yrs.	1.14	0.82-1.59
Rural	Multi	Age <75 yrs. vs. ≥75 yrs.	1.31	0.93-1.85
Urban	PHV	Age <75 yrs. vs. ≥75 yrs.	1.61	0.83-3.10
Rural	PHV	Age <75 yrs. vs. ≥75 yrs.	1.85	0.96-3.57
Urban	VTEP	Age <75 yrs. vs. ≥75 yrs.	1.49	0.90-2.47
Rural	VTEP	Age <75 yrs. vs. ≥75 yrs.	1.72	1.04-2.86
Urban	VTE	Age <75 yrs. vs. ≥75 yrs.	0.88	0.72-1.08
Rural	VTE	Age <75 yrs. vs. ≥75 yrs.	1.01	0.81-1.26
Urban	AF	Age <75 yrs. vs. ≥75 yrs.	0.87	0.76-1.00
Rural	AF	Age <75 yrs. vs. ≥75 yrs.	1.00	0.86-1.17
Age <75 yrs.	----------	Other vs. AF	0.83	0.73-0.95
Age ≥75 yrs.	----------	Other vs. AF	0.87	0.75-1.01
Age <75 yrs.	----------	Multi vs. AF	1.22	0.96-1.57
Age ≥75 yrs.	----------	Multi vs. AF	0.93	0.73-1.19
Age <75 yrs.	----------	PHV vs. AF	1.32	0.97-1.79
Age ≥75 yrs.	----------	PHV vs. AF	0.71	0.39-1.29
Age <75 yrs.	----------	VTEP vs. AF	1.07	0.70-1.61
Age ≥75 yrs.	----------	VTEP vs. AF	0.62	0.45-0.86
Age <75 yrs.	----------	VTE vs. AF	1.13	0.98-1.30
Age ≥75 yrs.	----------	VTE vs. AF	1.12	0.93-1.34

4.5.5 Sensitivity Analysis

In the sensitivity analysis, few changes to the odds ratios were observed when we modified the adherence thresholds to 60% and 100% (Table 4.15). The most notable differences were in the estimates for PHV (80% threshold OR 0.72, 95% CI 0.40-1.30; 100% threshold OR

1.07, 95% CI 0.58-1.97, among subjects age ≥75 years) and VTEP (60% threshold OR 0.82, 95% CI 0.60-1.12; 100% OR 1.24, 95% CI 0.92-1.69, among subjects age <75 years); however, the clinical importance of these differences is not known.

Table 4.15 Sensitivity Analysis of 80% Adherence Threshold - Parameter Estimates of Full Model Compared to 60% and 100% Adherence Thresholds

	80% threshold		60% threshold		100% threshold	
Effect	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Intercept	2.12	0.66 - 6.82	10.26	3.13 - 33.61	0.86	0.23 - 3.24
Age (<75 yrs.)	---	---	---	---	---	---
Sex (Female)	1.12	1.03 - 1.22	1.07	0.98 - 1.16	1.06	0.94 - 1.18
Rural	---	---	---	---	---	---
Income quintile						
2 vs. 1	1.09	0.96 - 1.24	1.20	1.05 - 1.37	1.08	0.91 - 1.29
3 vs. 1	1.04	0.91 - 1.18	1.20	1.06 - 1.37	1.06	0.89 - 1.26
4 vs. 1	1.04	0.91 - 1.18	1.14	0.99 - 1.30	1.02	0.85 - 1.23
5 vs. 1	1.14	0.99 - 1.31	1.19	1.03 - 1.37	1.15	0.96 - 1.39
Physician visit						
12-18 vs. 0-11	1.12	0.97 - 1.28	1.13	0.98 - 1.29	1.07	0.88 - 1.30
19-25 vs. 0-11	1.28	1.09 - 1.50	1.34	1.14 - 1.57	1.24	0.99 - 1.56
26-36 vs. 0-11	1.32	1.11 - 1.56	1.48	1.24 - 1.78	1.24	0.97 - 1.57
≥37 vs. 0-11	1.58	1.29 - 1.92	1.63	1.33 - 2.00	1.64	1.25 - 2.15
Hospitalization						
1 vs. 0	0.94	0.84 - 1.05	0.97	0.87 - 1.09	0.97	0.83 - 1.14
2 vs. 0	0.87	0.75 - 1.01	0.90	0.77 - 1.06	0.90	0.73 - 1.11
≥3 vs. 0	0.72	0.60 - 0.86	0.80	0.67 - 0.96	0.80	0.62 - 1.03
Charlson						
1 vs. 0	1.00	0.90 - 1.11	0.98	0.87 - 1.09	0.88	0.76 - 1.02
2 vs. 0	0.84	0.73 - 0.95	0.93	0.81 - 1.06	0.81	0.68 - 0.97
≥3 vs. 0	0.89	0.78 - 1.03	0.92	0.80 - 1.06	0.76	0.62 - 0.92
Diagnoses						
7-10 vs. 0-6	1.09	0.96 - 1.25	1.13	0.99 - 1.30	1.04	0.86 - 1.25
11-16 vs. 0-6	0.97	0.82 - 1.14	0.99	0.84 - 1.18	0.93	0.74 - 1.16
≥17 vs. 0-6	0.90	0.74 - 1.10	0.89	0.72 - 1.10	0.75	0.57 - 0.99
Prior diabetes						
No vs. Yes	1.13	1.02 - 1.26	1.25	1.12 - 1.39	1.05	0.90 -1.22
Prior stroke						
No vs. Yes	0.87	0.73 - 1.04	0.94	0.79 - 1.12	0.90	0.69 - 1.17
CV drugs						
1 vs. 0	1.05	0.90 - 1.22	1.17	1.00 - 1.38	1.00	0.82 - 1.21
2 vs. 0	1.08	0.93 - 1.26	1.23	1.05 - 1.44	1.01	0.82 - 1.24
3 vs. 0	1.12	0.95 - 1.31	1.23	1.05 - 1.45	1.08	0.88 - 1.34
≥4 vs. 0	1.14	0.99 - 1.32	1.22	1.05 - 1.42	1.15	0.95 - 1.40
Non-CV drugs						

	80% threshold		60% threshold		100% threshold	
Effect	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
1 vs. 0	0.93	0.84 - 1.02	0.95	0.86 - 1.04	0.93	0.82 - 1.06
2 vs. 0	0.99	0.88 - 1.12	0.86	0.76 - 0.97	1.02	0.87 - 1.20
≥3 vs. 0	0.77	0.67 - 0.89	0.80	0.69 - 0.92	0.97	0.80 - 1.17
Pract. Type						
GP vs. SP	2.74	0.89 - 8.49	2.81	0.91 - 8.68	2.77	0.79 - 9.78
Indication						
Other vs. AF	---	---	---	---	---	---
Multi vs. AF	---	---	---	---	---	---
PHV vs. AF	---	---	---	---	---	---
VTEP vs. AF	---	---	---	---	---	---
VTE vs. AF	---	---	---	---	---	---
Follow-up (days)						
91-180 vs. 35-90	0.16	0.13 - 0.20	0.09	0.06 - 0.12	0.15	0.13 - 0.18
181-365 vs. 35-90	0.09	0.08 - 0.11	0.04	0.03 - 0.05	0.06	0.05 - 0.07
366-730 vs. 35-90	0.06	0.05 - 0.07	0.02	0.02 - 0.03	0.02	0.02 - 0.03
≥731 vs. 35-90	0.04	0.03 - 0.04	0.02	0.01 - 0.02	0.00	0 - 0.01
Recent vs. new VKA use	0.80	0.71 - 0.91	0.84	0.74 - 0.96	1.11	0.92 - 1.33
Index year						
2005-06 vs. 03-04	1.05	0.95 - 1.17	0.95	0.85 - 1.06	1.11	0.95 - 1.30
2007-08 vs. 03-04	1.19	1.07 - 1.34	1.14	1.02 - 1.28	1.06	0.90 - 1.25
2009-10 vs. 03-04	1.18	1.03 - 1.34	1.17	1.01 - 1.35	1.05	0.89 - 1.24
Age*Indication						
*<75 yrs. *other*	---	---	---	---	---	---
*<75 yrs. *multi*	---	---	---	---	---	---
*<75 yrs. *PHV*	---	---	---	---	---	---
<75 yrs. VTEP*	---	---	---	---	---	---
*<75 yrs. * VTE*	---	---	---	---	---	---
Age *Urban/Rural	---	---	---	---	---	---
*<75 yrs.*Rural*	---	---	---	---	---	---

--- ORs not reported for interaction terms.

5 DISCUSSION

This retrospective cohort study examined adherence to INR testing among 17,388 individuals in Saskatchewan receiving anticoagulation with VKA medications between 2003 and 2010. The most frequently identified indications for VKA therapy were AF (34%) and VTE (14%), accounting for almost one-half of all patients examined. Altogether, 42% of the studied population resided in rural areas and virtually all patients (99%) appeared to be monitored by a general practitioner. Following the first dispensation for a VKA, the median interval until the first INR claim date was 26 days. During a median follow-up of 514 days, 50% of patients exhibited at least 74% adherence to INR testing if a 4-week interval was used as the reference standard. However, the estimated median adherence increased dramatically to 98% when the benchmark for optimal testing was lengthened to every 12 weeks, suggesting that most gaps in testing occurred during intervals that were between 4 and 12 weeks long. Further, very few cases of non-persistence to INR testing were identified, suggesting most patients continue testing while receiving VKAs, albeit sometimes at a lower frequency. The most prominent risk factors for non-adherence to INR monitoring appear to be rural residence and duration of VKA therapy.

The median adherence to INR testing (74%) using a 4-week test interval is lower than what has been reported in several studies, and only 44% of subjects achieved at least 80% adherence. It has been estimated that between 70% and 90% of VKA patients were monitored at least monthly in previously published study populations (52,72,82). However, these results may not reflect real world practice because these data were collected from a physician questionnaire (82), from a commercially insured population (52), or had a short duration of follow-up (72). Although the study cohort we identified from Saskatchewan was not testing as frequently as published estimates, median adherence in our cohort approached 100% when a 12-week testing interval was used as the reference standard. Also, when a more strict definition of continuous VKA therapy was used to define the follow-up period (51 days vs. 150 days), median adherence improved to 90%. The result of this sensitivity analysis suggests that a portion of INR non-adherence identified in the primary analysis may have been misclassified due to temporary discontinuations of VKA therapy when INR monitoring was not required. Finally, virtually no

evidence of non-persistence to INR monitoring could be identified. It would seem that patients do not quit INR testing until the VKA has been discontinued.

Based on the results from the primary analyses and sensitivity testing, it would appear that VKA therapy is being regularly monitored. However, it must be recognized that the study cohort was made up of individuals with at least one INR monitoring claim. In fact, almost 50% of all eligible episodes were excluded due to no recorded physician service claim for INR testing during the entire duration of VKA therapy. Although these patients may represent a complete lack of adherence to INR monitoring, it is also possible they are being managed by prescribers who are not reimbursed by the fee-for-service model. Alternatively, some practitioners may not bill for anticoagulation monitoring. Future studies should attempt to capture actual INR testing claims through laboratory databases in order to discriminate between these possible scenarios. At the time of this study, laboratory data was not accessible.

One of the most striking predictors of adherence in the multivariable model was duration of VKA use. The median adherence of patients in the first 3 months of VKA therapy was 86% compared to 62% beyond 2 years of therapy. The only other study to have investigated this association did not find that the length of VKA therapy was a predictor of non-adherence (OR 1.00, 95% CI 0.99-1.01) (94). However, a key difference is that our cohort was made up of mostly new users to VKA therapy. Therefore, declining adherence could be partly explained by the discontinuation of VKA therapy in patients who could not achieve stable INR levels early on. Thus, over time the patients that remain on therapy may have relatively stable responses to VKA medications and require less frequent INR testing. Stable VKA therapy is now an accepted reason to extend INR testing intervals as long as 12 weeks (49). At the time of proposing this project, INR testing was recommended at 4-week intervals regardless of previous testing results (1).

Rural residence was significantly associated with lower adherence to INR monitoring. Approximately one-third of rural residents achieved the threshold for optimal adherence, compared to one-half of urban residents. A possible explanation of poor adherence in this subgroup could be reduced access to testing facilities or a shortage of physicians in rural centers. More research would be needed to understand the exact nature of this association. The current data was restricted to two levels of residence, urban and rural only. Urban residence was defined as a Census Metropolitan Area or Census Agglomeration according to Statistics Canada (127).

Ideally, it would be useful to identify the locations of laboratory testing facilities and healthcare providers to determine if access was indeed the underlying cause of this association. Also, it is possible that rural residence may be a marker of other patient characteristics such as low socioeconomic status (105).

Despite the theoretical challenges with monitoring INR levels in rural areas, it appears that VKA therapy is frequently prescribed in this population because a relatively large proportion of the study cohort were rural residents (42%). A recent study suggests that there may be a greater risk of using anticoagulants in patients residing in rural areas. Shepherd and colleagues reported that the risk of death due to an adverse drug reaction was twice as high in rural areas compared to urban centers, and that anticoagulants were among the most responsible drug classes (141). It would be of interest to investigate if poor adherence to INR testing in rural areas translates into adverse health outcomes.

Our results suggest that subjects with an indication of VTEP or PHV may have an increased odds of adherence compared to those with AF. Median adherence was approximately 20% better among subjects with PHV (88.4%) and VTEP (90.5%) compared to those with AF (70.9%). This observation might be partly explained by the shorter duration of follow-up in these groups. The median duration of follow-up for subjects with AF was 755 days, compared to only 107 days with VTEP and 259 days for PHV. Shorter duration of use for VTEP and PHV are expected given that the excess risk of clotting may be temporary following orthopedic surgeries (20) and procedures for bioprosthetic valve replacement (19). Nonetheless, the high frequency of good adherence in the PHV group is reassuring given that many of these patients require a greater intensity of anticoagulation (i.e., have a higher INR target) compared to other indications (19).

5.1 Limitations

To our knowledge this descriptive analysis is the first to examine adherence to INR testing in a real-world population. Despite the great potential to understand VKA use, there are several limitations to consider. Most notably, physician fee-for-service claims for anticoagulant monitoring were used as a proxy for INR testing. As a consequence, a large number of episodes were excluded because no INR claims were recorded in the MSB. There are a variety of situations in which a subject could have been measuring their INR where it was not captured,

including testing at anticoagulation clinics, during periods of hospitalization, monitoring by a salaried physician, and where fee-for-service physicians might not submit a claim at all. Due to limitations in the data source, at least one INR claim was required to rule out these other scenarios. The results of this study must be interpreted with caution because it is possible that many patients receive VKA medications without INR monitoring. Certainly, inclusion of these patients would drastically modify the results observed in the current study cohort. It is anticipated that laboratory testing results will become available in the future. At that time, these data should be re-analyzed using the actual INR test results for all patients, regardless of physician claim status.

Another concern was the high number and proportion of VKA episodes that did not meet any of the case definitions for a disease group (29%). Several different strategies were used to attempt to capture a common indication for these missed episodes, as discussed in the results' section. These included a review of the frequency of diagnostic codes in the DAD and the MSB near the date of the first VKA dispensation, and expanding the criteria for an AF diagnosis to capture records in the prior year. However, none of these methods successfully identified a predominant diagnosis. Given that the records from emergency room (ER) visits were not available, our speculation is that a number of these subjects could have been diagnosed with a DVT in the ER and never admitted to the hospital. Capturing ER visit records and diagnoses would be the next recommended step to identify reasons for VKA therapy among study patients.

There are limitations to several of the explanatory variables we used in our models. We used validated case definitions wherever possible to categorize subjects based on their indication, but none of these were specifically validated in a population of anticoagulation users. Both income quintile and area of residence were assigned based on the subject's dissemination area from the 2006 Statistics Canada Census, and are not reported for each individual. Subjects were considered urban residents if they were living in a Census Metropolitan Area or Census Agglomeration with 10,000 or more people (127), while all others were categorized as rural. One limitation of this is that the definition of rural resident does not consider the extent of isolation or proximity to health services. Future work should attempt to subdivide this population based on travel distance to a general practitioner or hospital.

There were challenges to the assignment of VKA exposure that could have influenced our findings as well. Our definition for the discontinuation of VKA therapy is complicated by frequent dose adjustments, which make it difficult to estimate a days' supply. Also, refill compliance measures are not useful for drugs with frequent dosage changes (114). We addressed this by performing sensitivity analyses around the definition of discontinuation. The gaps between INR measurements could also be a result of the temporary discontinuation of the VKA, as suggested by van Walraven et al. (8). This could inflate the CMG, and ultimately underestimate adherence to INR monitoring. Lastly, we did not remove the time that subjects spent in hospital from their follow-up. Given that physician claims would not be captured over these time periods, this could also underestimate adherence.

The final limitation to consider is that the 80% adherence threshold has not been validated against outcomes. However sensitivity analyses were conducted around this level, and the estimates did not change noticeably. Future work could consider the clinical impact of different thresholds of INR adherence. Prior research has suggested that non-adherence to INR testing increases the risk of thromboembolism by approximately 50% compared to good adherence. However, in this study subjects were considered non-adherent if they missed only 2 consecutive scheduled INR tests at the anticoagulation clinic at which they were followed (94). This definition does not provide a measure of the extent of non-adherence as the CMG does. It would be of interest to determine if varying levels of adherence affect clinical outcomes differently.

6 CONCLUSION

This study provides some of the first insights into the nature of anticoagulation monitoring among community living patients in Saskatchewan, most of who were not managed by specialty providers. Overall, adherence to INR testing appeared generally acceptable; especially when a 12-week testing interval was used as the reference standard. Moreover, very few patients quit INR testing until the VKA therapy had been terminated. An association between rural residence and poor INR testing adherence was observed, but the true nature of this association could not be determined. Further research into the determinants of INR adherence in rural versus urban settings should be conducted to identify specific targets for improving anticoagulation success in the province. Specifically, understanding the quality of INR testing will help inform the rational use of new oral anticoagulant medications that are very costly but can be administered without the need for regular testing.

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APPENDIX A – List of Cardiovascular and Non-cardiovascular Medications

Cardiovascular drugs			
Antihypertensive agents			
acebutolol	indapamide	telmisartan	minoxidil
amiloride/HCTZ	irbesartan	telmisartan/HCTZ	oxprenolol
amlodipine	irbesartan/HCTZ	timolol	pindolol
atenolol	lisinopril	timolol / HCTZ	pindolol/HCTZ
atenolol/chlorthalidone	lisinopril/HCTZ	trandolapril	prazosin
benazepril	losartan	triamterene/HCTZ	reserpine
candesartan	losartan/HCTZ	valsartan	reserpine/chlorthalidone
candesartan/HCTZ	metolazone	valsartan/HCTZ	reserpine / HCTZ
captopril	metoprolol	verapamil	reserpine/HCTZ/hydralazine
chlorthalidone	metoprolol/HCTZ	amiloride	spironolactone
cilazepril	nadolol	clonidine	spironolactone/HCTZ
cilazepril/HCTZ	nifedipine SR	debrisoquine	terazosin
diltiazem	perindopril	doxazosin	bumetanide
enalapril	perindopril/indapamide	guanethidine	ethacrynic acid
enalapril/HCTZ	propranolol	hydralazine	furosemide
eprosartan	propranolol / HCTZ	labetolol	triamterene
felodipine	quinapril	methyldopa	
fosinopril	quinapril/HCTZ	methyldopa/CTZ	
hydrochlorothiazide (HCTZ)	ramipril	methyldopa/HCTZ	
Cardiac agents			
amiodarone	erythrityl tetranitrate	nicardipine	propafenone
bisoprolol	flecainide	nifedipine regular	quinidine
carvedilol	isosorbide dinitrate	nimodipine (EDS)	sotalol
digoxin	isosorbide mononitrate	nitroglycerin	tocainide
disopyramide	mexiletine	procainamide	
Diabetes agents			
acarbose	insulin	repaglinide (EDS)	
acetohexamide	metformin	rosiglitazone (EDS)	
chlorpropamide	nateglinide (EDS)	tolbutamide	
gliclazide (NF)	phenformin		
glyburide	pioglitazone (EDS)		
Lipid lowering agents			
atorvastatin	lovastatin	cholestyramine	fenofibrate
cerivastatin	pravastatin	clofibrate	gemfibrozil
rosuvastatin	simvastatin	colestipol	niacin 500 mg tablet (nicotinic acid)
fluvastatin	bezafibrate (EDS)	ezetimibe	probucol
Anticoagulants			
dalteparin (EDS)	heparin	tinzaparin (EDS)	
enoxaparin (EDS)	nadroparin (EDS)		
Antiplatelets			
dipyridamole (EDS)	ASA	ticlopidine (EDS)	
dipyridamole/ASA (EDS)	clopidogrel (EDS)	sulfinpyrazone	

Non-cardiovascular drugs

Hormone replacement therapy			
oral conjugated estrogen	estradiol & norethindrone/estradiol (EDS)	estropipate	
conjugated estrogen/medroxyprogesterone	estradiol valerate	oral medroxyprogesterone	
oral and transdermal estradiol (EDS)	estradiol/norethindrone (EDS)	progesterone micronized (EDS)	
NSAIDs			
ASA cpd. With codeine	fenoprofen	mefenamic acid	rofecoxib (EDS)
celecoxib (EDS)	floctafenine	meloxicam (EDS)	sulindac
diclofenac	flurbiprofen	nabumetone (EDS)	tiaprofenic acid
diclofenac/misoprostol	ibuprofen	naproxen	tolmetin
diflunisal	indomethacin	phenylbutazone	zomepirac
etodolac (EDS)	ketoprofen	piroxicam	
Antidepressants			
amitriptyline	doxepin	moclobamide	escitalopram
amoxapine	fluoxetine	nefazodone	trazodone
bupropion (EDS)	fluvoxamine	nortriptyline	venlafaxine
citalopram	imipramine	paroxetine	duloxetine
clomipramine	maprotiline	trimipramine	desvenlafaxine
desipramine	mirtazapine	sertraline	
Antipsychotics			
chlorpromazine	mesoridazine	trifluoperazine	risperidone
flupenthixol	pericyazine	ziprasidone	clozapine (EDS)
fluphenazine	perphenazine	zuclopenthixol	olanzapine (EDS)
fluspirilene	pimozide	aripiprazole	
haloperidol	pipotiazine	paliperidone	
loxapine	prochlorperazine	quetiapine	
Glucocorticosteroids			
beclomethasone	budesonide	hydrocortisone	
betamethasone	budesonide / formoterol (EDS)	methylprednisolone	
cortisone	dexamethasone		
Migraine agents			
Cafergot-PB	flunarizine	rizatriptan	
dihydroergotamine mesylate	methysergide bimaleate (EDS)	sumatriptan	
ergotamine tartrate	naratriptan (EDS)	zolmitriptan	
ergotamine/caffeine	pizotyline		
ergotamine/cyclizine/caffeine	almotriptan		
Bisphosphonates			
alendronate (EDS)	etidronate/calcium	risedronate	
etidronate	pamidronate (EDS)	zoledronic acid	
Uric acid agents			
allopurinol	colchicine	probenecid	
Proton pump inhibitors			
esomeprazole (EDS)	omeprazole (EDS)	rabeprazole (EDS)	
lansoprazole (EDS)	pantoprazole (EDS)		

H2-receptor antagonists		
cimetidine	misoprostol	ranitidine
famotidine	nizatidine	ranitidine bismuth citrate
Other gastrointestinal agents		
lansoprazole/clarithromycin/amoxicillin (EDS)	pirenzepine	sucralfate
Transplant agents		
cyclosporine (EDS)	sirolimus (EDS)	
mycophenolate (EDS)	tacrolimus (EDS)	